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Archives of Internal Medicine

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# THE RELATION OF ACHLORHYDRIA TO PERNICIOUS ANEMIA *

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NEW YORK

Achlorhydria is the most constant symptom of pernicious anemia. Indeed, the reported cases of pernicious anemia in which hydrochloric acid was present are so few that doubt has been raised as to their validity. In my experience I do not recall an instance in which achlorhydria was absent. Cases in which hydrochloric acid was present eventually proved to be diseases other than pernicious anemia. Therefore, achlorhydria may be regarded as the most decisive differential sign in establishing the diagnosis of pernicious anemia.

Following Hunter, until recently achlorhydria was regarded as secondary and consequent to gastro-intestinal sepsis of unknown origin. With more intensive study, it becomes evident that this view is untenable for the following reasons: 1. If achlorhydria were secondary, one should expect occasionally in the course of the development of anemia to witness the gradual diminution of hydrochloric acid from normal to subacidity and finally to achlorhydria. But such a diminution has not been noted. At the first examination, achlorhydria is invariably present. 2. The acid never appears, no matter how long the remission. Martius first conceived that achlorhydria was primary and represented an element in the predisposing constitution of pernicious anemia. A host of additional observations made in the past decade indicate strongly that this conception is correct. 3. Achlorhydria precedes the development of pernicious anemia. Hurst [1] found achlorhydria long before the onset of the clinical evidences of pernicious anemia, once, twelve years previously. Since then numerous similar instances have been reported, such as the case of Faber [2] (ten years) and Sturtevant [3] (fourteen years). Riley [4] reported many such cases in which the duration was

* Submitted for publication, Nov. 26, 1930.

1. Hurst, Arthur F., and Stewart, Mathew J.: Gastric and Duodenal Ulcer, New York, Oxford University Press, 1929.

2. Faber, K., and Gram, H. C.: The Association of Achylia and Anemia of Different Types in Three Members of the Same Family, Arch. Int. Med. **34**: 827 (Dec.) 1924.

3. Sturtevant, M.: Achlorhydria Preceding Pernicious Anemia, J. A. M. A. **85**:1638 (Nov. 21) 1925.

4. Riley, W. H.: Achlorhydria Preceding Pernicious Anemia, J. A. M. A. **85**:1908 (Dec. 12) 1925.

from four to twenty-five years. Connor [5] referred to additional observations and reported three cases in which achlorhydria preceded pernicious anemia from two to eighteen years. This observation explains the frequency with which one obtains the history of diarrhea (gastrogenous) preceding the onset of pernicious anemia. Since achlorhydria often precedes pernicious anemia by a number of decades, the question arises whether achlorhydria and the consequent anemia are congenital and transmissible, and therefore familial characteristics.

A discussion of the entire relation of achlorhydria to these hereditary characters leaves much to be desired, for the gaps in the knowledge of the subject are huge. Even the discovery of the existence of alchlorhydria is not as simple as it appeared to be when the Ewald meal was the standard test. The fractional test meal has considerably reduced the number of true cases of achlorhydria; furthermore, this residuum has again been shrunken by the discovery that with the neutral red reaction and histamine, hydrochloric acid may be demonstrated when it was previously absent. All previous statistics as to the percentage incidence of achlorhydria in various maladies and under normal conditions therefore require complete revision.

## FAMILIAL INCIDENCE OF ACHLORHYDRIA AND OF PERNICIOUS ANEMIA

No statistics are available that are based on modern methods of examination. The older statistics based on the Ewald meal are obviously too high. In 1921, Bennet and Ryle [6] found an incidence of 4 per cent with the fractional method. In 1924, Baird, Campbell and Hern [7] reported an incidence of 3.5 per cent with the same method. I do not know what the percentage of incidence would be with neutral red or histamine. Furthermore, as Connor [5] and others have shown that the percentage of achlorhydria increases in each decade, a "normal" figure for all ages offers only indifferent information. Therefore, sound statistics on the normal incidence of achlorhydria are much desired. I am told by Dr. Asher Winkelstein, chief of the gastro-intestinal clinic at Mount Sinai Hospital, New York, that in his clinic when repeated and varied fractional test meals are used and a reaction to combined neutral red and histamine is elicited, the incidence of achlorhydria is 0.21 per cent. He supplied me with the following statistical data compiled in the achylia gastrica statistics in the gastro-intestinal clinic of Mount Sinai Hospital: 1. All of these cases were true achlorhydria as proved

5. Connor, H. M.: Hereditary Aspect of Achlorhydria in Pernicious Anemia, J. A. M. A. **94**:606 (March 1) 1930.

6. Bennet, T. I., and Ryle, J. A.: Guy's Hosp. Rep. **71**:268, 1921.

7. Baird, M. McC.; Campbell, J. H. M., and Hern, J. R.: Guy's Hosp. Rep. **74**:339, 1924.

by repeated test meals and tests with neutral red and histamine. 2. The symptoms were vague—diarrhea, constipation, abdominal pains, anemia, and possible disease of the gallbladder. 3. Proved cases of pernicious anemia, subtotal gastrectomy, carcinoma, etc., were not included. In 2,348 consecutive patients, 49 cases occurred, making the incidence 0.21 per cent; there were 25 males and 24 females.

The age incidence was as follows: from 20 to 30 years of age, 6 cases; from 30 to 40, 9 cases; from 40 to 50, 20 cases; from 50 to 60 4 cases, and from 60 to 70, 8 cases.

There is no doubt that achlorhydria with or without pernicious anemia is frequently familial. In 20 or 30 cases of pernicious anemia, Martinez [8] found achlorhydria in both parents and in 2 or 3 members of the family. In another family, the great grandmother, the grandmother, 4 grandchildren and 5 of the 13 greatgrandchildren had achlorhydria. In a small series of cases studied with Dr. Crohn some years ago, it was found that about 40 per cent of the apparently normal children of patients with pernicious anemia had achlorhydria. Hurst [9] reported a number of cases of achlorhydria in the relatives of patients who had pernicious anemia or combined sclerosis. Dorst [10] reported a family in which 5 members had pernicious anemia, while 4 of the remaining apparently normal members showed achlorhydria. Weinberg [11] examined 22 children and 2 sisters of 12 patients with pernicious anemia; 9 of the children and a sister showed achlorhydria. In another family, 3 of the 4 children, aged 6, 10 and 14, showed achlorhydria. Mustelin [12] reported a family in which a case of pernicious anemia occurred in each of three generations. A fair proportion of other members of the family revealed achlorhydria, some of whom presented an anemia of the chlorotic type. Mustelin regarded achlorhydria as a dominant hereditary character.

The entire subject has recently been studied by Connor, who used the extensive resources of the Mayo Clinic. With the fractional test meal alone he found an incidence of 14.2 per cent of the cases of achlorhydria in a series of 5,000 patients suffering from various diseases exclusive of pernicious anemia. Of 154 blood relatives of persons with pernicious anemia, the gross percentage of those with achlorhydria was 25.9 per cent. Connor expressed the belief that more than half of these blood relatives were healthy, so that the high incidence of achlorhydria is significant. Of especial significance, brought out by Connor's studies, is the fact that the proportion of achlorhydria in these

8. Martinez, P. N.: Med. ibera **1**:118, 1927.
9. Hurst, A. F.: Lancet **1**:111, 1923.
10. Dorst, S. E.: Am. J. M. Sc. **172**:173, 1926.
11. Weinberg, F.: Ztschr. f. ang. Anat. **6**:289, 1920.
12. Mustelin, O.: Acta med. Scandinav. **56**:411, 1922.

blood relatives rises with each decade, except in the sixth (see table).

What the drop in the seventh decade signifies was not apparent to Connor. He concluded:

> From these figures it seems to be strongly indicated that, when correction is made for age and sex, achlorhydria has a distinct tendency to occur more frequently among blood relatives of patients who have pernicious anemia than among normal persons or among persons who have a great variety of other diseases. This may mean that there is an inherited tendency to the occurrence of achlorhydria in many blood relatives of patients with pernicious anemia over and above any such tendency among patients having various other diseases, and even among those having gastro-intestinal symptoms. It seems unlikely, however, that the achlorhydria itself is inherited, but that the tendency to its development later may be an inherited factor.

*Achlorhydria According to Age Groups Among Blood Relatives of Patients with Pernicious Anemia (Connor)*

| Age in Decades | Relatives | Subjects with Free Hydrochloric Acid | Subjects with Achlorhydria | Proportion with Achlorhydria, per Cent |
|---|---|---|---|---|
| 10 to 19 | 13 | 12 | 1 | 7.6 |
| 20 to 29 | 37 | 32 | 5 | 13.5 |
| 30 to 39 | 45 | 36 | 9 | 20.0 |
| 40 to 49 | 26 | 14 | 12 | 46.1 |
| 50 to 59 | 17 | 12 | 5 | 29.4 |
| 60 to 69 | 14 | 6 | 8 | 57.1 |
| 70 to 79 | 2 | 2 | .. | .... |
| Total | 154 | 114 | 40 | 25.9 |

The observations of Connor are significant, even if, as seems likely, the absolute values will be somewhat less when more precise methods of determining achlorhydria are employed. Their greatest significance lies in the light that they throw on the constitutional element in pernicious anemia. This will be more fully evident after the discussion of the heredity aspects of pernicious anemia.

## THE HEREDITY OF PERNICIOUS ANEMIA

There is no doubt that pernicious anemia is not a congenital disease. Pernicious anemia is practically unknown in the first decade and extremely rare in the second. Naegeli [13] reported cases of pernicious anemia in 3 children, aged 8, 11 and 12 years. He expressed the belief that the case of Escherich, who reported pernicious anemia in a child of 4, is not valid because the blood criteria were not sufficiently precise. In the carefully studied series of cases reported by Willson and Evans [14] the youngest patient was between 10 and 20 years

13. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Lehrbuch der morphologischen Hämatologie, Leipzig, Veit & Company, 1923.

14. Willson, C. R., and Evans, F. A.: Bull. Johns Hopkins Hosp. **35**:38, 1924.

of age. In 111 cases, none occurred between the ages of 1 and 10; 0.9 per cent of the cases occurred between 10 and 20; 2.7 per cent, between 20 and 30; 23 per cent, between 40 and 50, and 33 per cent, between 50 and 60. The decline of the rate of pernicious anemia in people past 60 years of age is probably due to the fact, as Meulengracht [15] said, that most patients die of anemia before they reach this age. The familial character of pernicious anemia has been clearly established. I have seen a number of such cases, while numerous instances were reported by Barker,[16] Gram,[17] Faber and Gram,[2] Patek,[18] Grinker,[19] Dorst,[10] Meulengracht,[20] Hurst,[1] Weinberg,[11] Tscherning,[21] Gulland and Goodall.[22] Tichter [23] found a history of heredity in 4.2 per cent of 140 patients with pernicious anemia admitted to the Eppendorf Krankenhaus. In a series of 90 patients, Carey [24] found that 10 gave a history of probable pernicious anemia in the family. A patient told me that pernicious anemia was diagnosed in 5 members of her family in three generations. Levine and Ladd [25] found that pernicious anemia was familial in 6 per cent of their cases. Studies on the hereditary nature of pernicious anemia are still incomplete, because the precise diagnosis of pernicious anemia has been developed comparatively recently, and it will require observations on three and more generations before it can be determined (1) whether pernicious anemia is always hereditary or whether it is a biologic sport; (2) whether it follows the mendelian law, and (3) whether it is a dominant or a recessive character. Numerous instances have been reported in which pernicious anemia occurred in parent and child, but Mustelin's case is apparently the only instance of pernicious anemia in three generations, a grandmother aged 69, a daughter aged 44, and a granddaughter aged 25. The difficulty in determining accurately the hereditary incidence is due to the fact that it will never be known whether pernicious anemia might not have developed in those who have died in early life. Bringing these facts con-

15. Meulengracht, C.: Am. J. M. Sc. **169**:177, 1925.

16. Barker, L. F.: The Etiology and Treatment of Pernicious Anemia, J. A. M. A. **87**:80 (July 10) 1926.

17. Gram, H. C.: Ugesk. f. læger **91**:1135, 1929.

18. Patek, A. J.: Family Pernicious Anemia, J. A. M. A. **56**:1315 (May 6) 1911.

19. Grinker, Roy R.: Pernicious Anemia, Achylia Gastrica and Combined Cord Degeneration and Their Relationship, Arch. Int. Med. **38**:292 (Sept.) 1926.

20. Meulengracht, C. R.: Folia haemat. **32**:300, 1926.

21. Tscherning, R.: Deutsche med. Wchnschr. **52**:707, 1926.

22. Gulland, G. L., and Goodall, A.: The Blood, ed. 3, Edinburgh, W. Green & Son, 1925.

23. Tichter: Inaugural Thesis, Berlin, 1927.

24. Carey, J. B.: Minnesota Med. **9**:385, 1926.

25. Levine, S. A., and Ladd, W. S.: Bull. Johns Hopkins Hosp. **32**:254, 1921.

cerning the hereditary and familial incidence of pernicious anemia in accord with the corresponding incidence of achlorhydria, one may infer that there is a strong constitutional element in pernicious anemia in the sense that there is a transmissible background for the disease and that an important feature in this element is the tendency to acquire achlorhydria. Curiously, this element differs from other constitutional characteristics in that achlorhydria itself is not transmissible. Comprehensive statistics on the gastric contents of newly born infants are lacking, but pediatricians testify that achlorhydria in infants is extremely rare. Even in early childhood achlorhydria is probably extremely rare. Copeman and Hill [26] reported 7 cases of achlorhydria in 66 normal children between the ages of from 12 to 15. Katsch [27] collected only a few cases. One was that of a child, aged 12. He quoted Schmidt,[28] who claimed to have seen achlorhydria in association with various degenerative stigmas, and Albu [29] who reported a number of cases occurring in patients below the age of 7.

### THE RELATION OF ACHLORHYDRIA TO BOTHRIOCEPHALUS LATUS ANEMIA

The hematologic and clinical picture of pernicious anemia and that of *Bothriocephalus* anemia are identical, even in respect to achlorhydria. The question arises: Is achlorhydria the result, or did it precede the infestation? One cannot definitely answer this question for the obvious reason that studies of the gastric contents of patients previous to the infestation with the worm are not available. But there is abundant circumstantial evidence that, as with cryptogenetic pernicious anemia, the so-called *Bothriocephalus* variety shows a strong familial tendency. It is well known that in certain countries, Finland for instance, where infestation with *Bothriocephalus* is extremely common, the incidence of pernicious anemia in these persons is small, being only 1 per cent according to Tallquist.[30] Now Schaumann,[31] whose studies on *Bothriocephalus* anemia are the most comprehensive extant, found that in only 1 of 11 cases studied the gastric contents reacted to the phloroglucin-vanillin test. So far as I am aware, no mass studies on the gastric contents in *Bothriocephalus* anemia have been done since those of Schaumann, but judging from the scattered casuistic reports, achlorhydria has always

26. Copeman and Hill: Lancet **1**:718 (April 6) 1929.

27. Katsch, G.: Handbuch der inneren Medizin, Berlin, Julius Springer, 1926, vol. 3, part 1.

28. Schmidt, quoted by Katsch (footnote 27).

29. Albu, quoted by Katsch (footnote 27).

30. Tallquist: Ztschr. f. klin. Med. **61**:427, 1907.

31. Schaumann: Zur Kenntnis der sogennannten bothriocephalus Anämie, Helsingfors, 1894.

been found. The case of Isaacs and Sturgis [32] is particularly interesting because not only did achlorhydria persist for five months after expulsion of the worm, but the mother of the patient had true primary pernicious anemia. I have been informed of another case observed in Hamburg in which achlorhydria was noted both before and after the expulsion of the worm. Therefore, the probability is strong that achlorhydria is as constant an observation in *Bothriocephalus* as in primary pernicious anemia. Schaumann's original observations on *Bothriocephalus* anemia, published in a monograph in 1894, are exceedingly valuable as a clinical and diagnostic exposition. He did a remarkable piece of work. In 1910,[33] he published a paper in which he reported a follow-up of the cases of *Bothriocephalus* anemia that he had observed between 1883 and 1893, that is, from seventeen to twenty-seven years previously. This report is most illuminating; it reveals that the constitutional element is as manifest in *Bothriocephalus* anemia as in cryptogenetic pernicious anemia. Even in his original publication, Schaumann, with remarkable acumen, suspected that there must be a constitutional element in *Bothriocephalus* anemia, because he could not understand why anemia developed in such a small percentage of patients infested with *Bothriocephalus*. First Schaumann found that a considerable number of his patients (17 per cent) died, even after the worm was expelled. He also found that true primary pernicious anemia later developed in 7 of his patients with *Bothriocephalus* anemia who were "cured" after expelling the worm. Furthermore, he found that in 24 of the families, at least 2 of the members revealed clinical evidences of pernicious anemia; in 15 the anemia was associated with infestation with *Bothriocephalus*; in 7, it was cryptogenetic, and in 2 families it was both cryptogenetic and bothriocephalic. He also found, as others have since, that achlorhydria persisted after the expulsion of the worm. Based on his observations, in all of his publications, even up to his most recent one in 1925, Schaumann [34] expressed the belief that there is a constitutional background for the disease. In the light of modern conception it is intriguing to think that it is only those patients with achlorhydria who acquire pernicious anemia after infestation with *Bothriocephalus*. Unfortunately, there are a considerable number of facts that make one skeptical as to whether *Bothriocephalus* has anything to do with the development of the pernicious anemia. These facts are presented in the following paragraphs.

32. Isaacs, R.; Sturgis, C. C., and Smith, M.: Tapeworm Anemia: Therapeutic Observations, Arch. Int. Med. **42**:313 (Sept.) 1928.

33. Schaumann: Deutsche med. Wchnschr. **36**:1218, 1910.

34. Schaumann and Saltzman: Handbuch des Krankheiten des Blutes und blutbildenden Organe, Berlin, 1925, vol. 2.

1. In certain areas of Finland where infestation with *Bothriocephalus* is extremely common, affecting from one quarter to one third of the population in certain districts, the number of patients in whom pernicious anemia develops is extremely small, less than 1 per cent according to Schaumann and Tallquist and at the most 0.5 per cent, according to Ehrström.[35]

2. If *Bothriocephalus* were an inciting agent of pernicious anemia, one should expect a much higher percentage of *Bothriocephalus* ane. ia as compared to the cryptogenetic variety in countries infested with *Bothriocephalus*. Even Schaumann and Saltzman's[34] statistics show that of 44,087 patients admitted to the Helsingfors Hospital, the total percentage with *Bothriocephalus* anemia was 0.74 and, with cryptogenetic anemia, 0.44, a difference that is not impressive. Even this narrow difference may be partly accounted for by the fact that the diagnosis depended on the finding of the eggs of the worm in the stool. Cases have been reported by Neubecker[36] and Meyer[37] in which the worm was never found after repeated antihelminthic therapy, despite the constant presence of eggs in the feces.

3. The development of the anemia bears no relation to the number of parasites. Schaumann and Saltzman reported a number of instances in which as many as 78 or even 90 worms were expelled, although the patient at no time had anemia.

4. Schaumann and Saltzman also reported the cases of patients who have overcome a so-called *Bothriocephalus* anemia and who years later became reinfected without pernicious anemia developing.

5. These authors and Runeberg[38] reported the cases of several patients in whom anemia improved spontaneously even before the worm was expelled. Sturgis and Isaacs reported a case of *Bothriocephalus* anemia in which the patient recovered under liver therapy before the worm was expelled. Saltzman[39] reported typical reticulocytic reactions in *Bothriocephalus* pernicious anemia after liver therapy, with abrupt improvement in the blood picture agreeing with the results obtained by liver therapy in cryptogenetic anemia. He expressed the belief, nevertheless, that tapeworm anemia seems more often resistant to liver therapy than does cryptogenetic anemia. Further studies on an extensive scale of the effect of liver therapy in so-called *Bothriocephalus* anemia as compared to therapy by expelling the worm are desirable.

6. The extraordinary clinical similarity between cryptogenetic and *Bothriocephalus* pernicious anemia, the fact that true pernicious anemia

35. Ehrström, R.: Ztschr. f. klin. Med. **105**:106, 1927.
36. Neubecker: Inaugural Thesis, Königsberg, 1898.
37. Meyer: Med. News **86**:633, 1905.
38. Runeberg: Deutsches Arch. f. klin. Med. **41**:304, 1887.
39. Saltzman, F.: Nederl. tijdschr. v. geneesk. **73**:4463, 1929.

is associated so commonly with *Bothriocephalus* anemia in families in which the latter is present, and that in Schaumann's collection of 14 "cured" cases of *Bothriocephalus* anemia the cryptogenetic variety developed in later years are circumstances that make one suspect that the two diseases are identical. Curiously, even the incidence of *Bothriocephalus* anemia according to decades corresponds precisely to that of the cryptogenetic variety (Schaumann). There are certain negative evidences.

7. *Bothriocephalus* is not the only parasite that has been brought into causal relationship with pernicious anemia; a host of other helminths have been reported as the "causes" of pernicious anemia, and curiously the number of such cases reported is proportionate to the frequency with which the parasite is encountered in man. Thus in the order of frequency, cases of pernicious anemia have been reported due to *Taenia saginata, Ascaris, Taenia solium, Trichocephalus dispar, Ancylostoma, Hymenolepis, Anguillula intestinalis, Lamblia intestinalis* and *Distoma hepaticum*. Wiemer and Derra[40] reported that 7.9 per cent of their patients with pernicious anemia gave a previous history of having had worms (mostly *Taenia* and *Ascaris*), and that the course of the disease was not influenced in the least in those in whom the worm was expelled. It is difficult to believe that the presence of these worms in patients with the blood picture of pernicious anemia represents more than the mere association, according to the law of chance, of two separate and unrelated conditions. Such associations are exceedingly common in medical practice, and often require considerable circumspection. It is now understandable why the helminthic origin of certain cases of pernicious anemia was first propounded in Finland. Outside of this country, the total number of reported cases is exceedingly small, according to Ehrström only 29, and practically all of these cases were imported.

Only one piece of evidence lends support to the belief that *Bothriocephalus* causes pernicious anemia, and that is the frequency with which cures are reported after expulsion of the worm. Schaumann claimed that in about 17 per cent of such cases failures occurred; others reported less, but apparently their testimony comes from insufficient observation and from a desire to make the etiologic relationship complete. From a rather careful perusal of the reported cases, I gather that the percentage of failures is larger than this optimism warrants. In most reported "cures" the subsequent history is not stated. With a disease of such a long life cycle as pernicious anemia, it is always possible that the disease passed into a stage of remission, an event that before liver therapy was more often spontaneous than otherwise, and that a proper "follow up" would reveal a much higher percentage of failures. Certainly the considerable number of "cured" cases of *Bothriocephalus*

40. Wiemer, P., and Derra, E.: Med. Klin. **24**:168, 1928.

anemias in which the cryptogenetic variety ultimately develops adds support to this view.

When all these facts are taken into consideration, it is apparent that a resurvey of the entire field of *Bothriocephalus* anemia is necessary. So far as the facts allow, one may justifiably say that it is not proved that *Bothriocephalus* is the origin of pernicious anemia. Ehrström denied such an origin entirely.

Tallquist's [41] experiment in which a lipoid substance derived from the proglottis of the *Bothriocephalus* worm caused a hemolytic anemia has not been confirmed by Hirschfeld,[42] Schminke [43] or Flury.[44]

### THE RELATION OF ACHLORHYDRIA TO OTHER ANEMIAS

*Relation to Secondary or Chlorotic Types of Anemia.*—Clinically, one is struck by the frequency of anemia of the secondary or chlorotic types in patients with achlorhydria. In a series of 207 cases of achlorhydria, Faber found pernicious anemia in 22. In 52 cases there was simple chlorotic anemia which he found extremely resistant to treatment. He did not believe that chlorotic anemia changed into pernicious anemia, but as it probably takes a considerable time for pernicious anemia to develop after achlorhydria has set in, this statement must not to be taken too seriously. Weinberg [45] reported the observations on the blood in 77 patients with achlorhydria. In 14 per cent, the hemoglobin was below 80 per cent; in 35 per cent, the red cell count was below 4,500,000; in 38 per cent, the color index was over 1, and in 60 per cent, the leukocytes were low. He frequently found normoblasts, myelocytes, myeloblasts and poikilocytes in patients in whom the hemoglobin was normal. He regarded these observations as representing the early phase of pernicious anemia. Mustelin reported achlorhydric members of families with pernicious anemia of the chlorotic type. Meulengracht described the case of a child with achlorhydria, a blood relative in a family in which pernicious anemia was present; examination showed: hemoglobin, 98 per cent; red cells, 3,000,000; color index, 1.25; megalocytosis; average red cell diameter, 8.8 mm.; leukopenia; bilirubinemia; urobilinuria, and glossitis. In 50 per cent of 134 patients with achlorhydria, Borgbjoerg and Lottrop [46] found that there was an anemia usually of the simple type and mild. In 22 the color index was over 1. Megalocytosis was found in 15 per cent, most often in patients

41. Tallquist: Ztschr. f. klin. Med. **61**:427, 1907.
42. Hirschfeld, quoted by Schaumann and Saltzman (footnote 34).
43. Schminke, W., and Flury, F.: Arch. f. exper. Path. u. Pharmakol. **64**: 126, 1910-1911.
44. Flury, F.: Arch. f. exper. Path. u. Pharmakol. **67**:275, 1911-1912.
45. Weinberg, F.: Deutsches Arch. f. klin. Med. **126**:447, 1918.
46. Borgbjoerg, A., and Lottrop, M. C.: Hospitalstid. **72**:745, 1929.

with a high hemoglobin value. They expressed the belief that a careful examination of the blood, especially in cases with a high percentage of hemoglobin, would probably reveal some cases of pernicious anemia in the early stage. Carey investigated 23 cases of achlorhydria. Three showed color indexes of over 1. The blood smears of those with a high index showed macrocytes and polychromasia. He also reported 4 cases in which achlorhydria and anemia had been demonstrated for various intervals of years before pernicious anemia developed. One case in which blood counts are tabulated had shown a high index, although anemia was hardly apparent. Kohn [47] examined the blood of 10 patients with achlorhydria proved by testing with neutral red. He found a high color index in 9. In a few cases there were myelocytes and in 1 a normoblast. I have observed a patient who for some months previous to the development of the typical hematologic picture of pernicious anemia showed an unexplainable secondary anemia.

The entire question centers around the following problems: 1. Does pernicious anemia eventually develop in all patients with true achlorhydria? As the majority of cases of pernicious anemia occur in the fourth and fifth decades, it will take an accurate study of a family with pernicious anemia covering three generations before this question can be answered. 2. What is the earliest blood picture in patients in whom pernicious anemia develops? Obviously, by the time the patient feels badly enough to present himself to the clinic, the disease may be considered already well advanced. If the few observations previously mentioned may be accepted, one gathers that the changes in the blood are already profound and various in what may be called the preclinical stage. But it is apparent that much further study is required to gain a proper perspective, not so much by casual examination, but more especially by studying the development of the changes in the blood from the earliest phases to the mature picture. Nothing is known, for instance, as to when megalocytosis, probably the more constant feature of the examination of the blood in pernicious anemia, arises in the preclinical stage.

*Relation of Artificial Achlorhydria to Anemia.*—The occasional reports of the hematologic pictures of pernicious anemia following artificial achlorhydria produced by complete resection of the stomach have suggested that achlorhydria bears some causal relation to anemia. Such reports are remarkably few, and a number of these will not pass criticism. In Moynihan's [48] patient, "severe anemia" developed three years after the resection for cancer. He had one remission, but died within a year. Autopsy revealed only an intense anemia and no recur-

47. Kohn, E.: Wien. klin. Wchnschr. **41**:1221, 1928.

48. Moynihan, B.: Lancet **2**:430, 1911.

rence. Hartmann [49] reported a well observed case of complete gastric resection for carcinoma. Achlorhydria was present before the operation. Two years later, the patient showed the hematologic evidences of pernicious anemia. Dennig [50] reported the case of a man, aged 41, in whom the typical blood picture of pernicious anemia with symptoms of the cord developed eight years after complete gastric resection for ulcer. He was "cured" by liver therapy, but died one year later from gangrene of the lung. Hochrein [51] reported 2 cases of resection of the stomach for cancer and ulcer, respectively. In the first patient the blood picture resembled pernicious anemia; in the second, a secondary anemia. Both cases responded to liver therapy. In Scheidel's [52] patient, pernicious anemia developed six years after a high and incomplete gastric resection. Liver therapy was successful. Morawitz [53] reported 3 cases of anemia following gastric resection. One showed the hematologic evidences of pernicious anemia; the second, secondary anemia, and the third, anemia of the aplastic variety. All of the patients responded well to liver therapy. Hurst spoke of 5 cases within his knowledge; 4 occurred following partial gastrectomy, and 1, after gastrojejunostomy. Castle [54] referred to 9 cases collected by Finney and Rienhoff,[55] in which complete gastrectomy was performed, the patients surviving for at least a year; in 2 (Hartmann and Dennig's cases) pernicious anemia apparently developed. The evidence favoring the development of pernicious anemia after complete gastrectomy is by no means complete. There is no reason why a common disease like pernicious anemia should not be associated with maladies so common as gastric carcinoma or ulcer. Furthermore, gastric cancer and ulcer are not infrequently treated by complete or nearly complete resection, so that the probability is likely, according to the law of chance, that pernicious anemia might occasionally seem to follow such an operation. Of course, it is essential for purposes of observation that the resection be complete in order to be sure that achlorhydria is complete. In 2 of 9 such cases quoted by Castle from Finney and Reinhoff's statistics (those of Hartmann and Moynihan), pernicious anemia developed, a percentage that is not very impressive, even granting that Moynihan's case is a valid one of pernicious anemia, which is doubtful. Of course, it is possible that after gastric resection a more

49. Hartmann, H. R.: Am. J. M. Sc. **162**:20, 1921.

50. Dennig, H.: München. med. Wchnschr. **76**:633, 1929.

51. Hochrein, M.: München. med. Wchnschr. **76**:1327, 1929.

52. Scheidel, H.: Med. Klin. **26**:247, 1930.

53. Morawitz, P.: Med. Klin. **26**:261, 1930.

54. Castle, W. B., quoted by Sturgis, C. C., and Isaac, R.: Desiccated Stomach in the Treatment of Pernicious Anemia, J. A. M. A. **93**:747 (Sept. 7) 1929.

55. Finney and Rienhoff, quoted by Castle, W. B.: Brit. M. J. **1**:1120, 1929.

prolonged period of observation would reveal a higher percentage developing pernicious anemia. More suggestive is the case of Du Bois reported by Castle in which a blood picture of pernicious anemia with achlorhydria developed in a girl aged 13, an age most unusual for the appearance of this disease. Although she responded to liver therapy, other symptoms necessitated an operation, when a tight stenosis of the pylorus due to enlarged tuberculous glands was found. Castle expressed the belief that achlorhydria may have been due to stenosis and that pernicious anemia was the result. It would be interesting to follow this patient to determine whether she eventually maintained the clinical evidences of pernicious anemia. Altogether one cannot make a very convincing argument concerning the development of pernicious anemia from an artificial achlorhydria obtained by complete resection, even though such a contention seems reasonable. To settle this problem, better and more extensive observations are necessary.

*Relation of Achlorhydria to the Severe Anemia of Pregnancy.*—It is impossible to discuss this relationship with even any attempt at precision because the gaps in the reported observations are large. The not uncommon secondary and chlorotic types of anemia are not of interest in this paper; I shall deal with only the anemias that resemble the pernicious type. Apparently these cases can be divided into those in which achlorhydria is present and those in which it is not. Such anemias may arise in any month of pregnancy and even after parturition. Anemia may arise after the first pregnancy; indeed, Schaumann and Saltzman [34] hold that it is more common in primipara than in multipara. It may recur after each pregnancy, but Esch,[56] Gurowitch [57] and Naegeli [13] reported cases in which a subsequent pregnancy or pregnancies were not followed by anemia. The early cessation of pregnancy apparently has no effect on anemia. McSwiney [58] and Balfour, Wills and Mehta [59] described a form of anemia that is common in India, occurring more frequently in pregnant than in nonpregnant women. The color index is high; the blood smear shows a few nucleated red cells, mostly normoblasts; free hydrochloric acid is present, and there are no neurologic or lingual signs. It is the consensus that the severe anemias of pregnancy respond admirably to treatment with liver.

There can hardly be any question that some of the reported cases of pernicious anemia following pregnancy represent chance associations of two rather common conditions. I saw such a case several years ago. The clinical picture of pernicious anemia was perfect, even as to glos-

56. Esch, P.: Zentralbl. f. Gynäk. **50**:857, 1926.

57. Gurowitch: Inaugural Thesis, Zurich, 1912.

58. McSwiney, S. A.: Indian M. Gaz. **62**:487, 1927.

59. Balfour, M. I.; Wills, L., and Mehta, M. M.: Indian J. M. Research **17**:777, 1930.

sitis and achlorhydria, and the patient responded nicely to treatment with liver. Of course, it is possible that pregnancy is the inciting factor in patients who have achlorhydria. A complete study and follow-up are necessary before a differentiation can be made between cases of true Addisonian anemia and those that are not.

*Relation of Achlorhydria to the Anemia of Sprue.*—Here again knowledge is deficient. It is well known that not only secondary anemia but a clinical picture closely resembling that of pernicious anemia is often associated with sprue; that is, these patients show the typical hematologic picture, achlorhydria and glossitis. According to Wood,[60] changes of the cord occur often in sprue, but less frequently than in the cryptogenetic variety. It is difficult to obtain an estimate in mass figures of the frequency in which achlorhydria occurs in sprue, not only because the determinations were made before modern methods were devised, but because there are no available statistics. Wood said that it occurs "more often than one would infer"; that it occurs in the late phases of the disease, and that free hydrochloric acid is present in the early stages. In 6 of 13 cases Bovaird[61] found anacidity; in 1 patient subacidity was noted and 6 were normal. Newham, Morris and Manson-Bahr[62] reported achlorhydria in 2 of 5 observed cases of sprue. I am informed that in Porto Rico the percentage of achlorhydria in sprue is about 25 per cent. Hegler's[63] report is interesting, because his patient in whom a clearcut picture of pernicious anemia with achlorhydria developed had had hyperchlorhydria two years earlier. An investigation by the Bombay Commission[64] revealed that about one half of the patients examined had achlorhydria.

In order to determine the relation of achlorhydria to the anemia of sprue, one would have to know certain other data. For instance, does achlorhydria develop in sprue or is it a precursor of the disease? Does anemia occur in sprue only in the cases in which achlorhydria is present? In true cases in which recovery occurs, does the achlorhydria return? Why is it that liver therapy as a rule is unsuccessful in the treatment for the anemia of sprue? Probably the reason is that the anemia of sprue and of pernicious anemia are entirely separate diseases and that one does not pass into the other and vice versa, no matter how close the clinical resemblance may be. At all events, these are the problems that must be left for future study.

60. Wood, E. J.: Am. J. M. Sc. **169**:28, 1925.

61. Bovaird, D.: A Study of Tropical Sprue, or Psilosis, J. A. M. A. **77**:753 (Sept. 3) 1921.

62. Newham, H. B.; Morris, R. M., and Manson-Bahr, P. H.: Lancet **2**:269, 1926.

63. Hegler, C.: Deutsche med. Wchnschr. **54**:1505, 1928.

64. Report of Bombay Bacteriological Laboratory for the Year 1924, Bombay, 1925.

## MECHANISM OF ACHLORHYDRIA ON ERYTHROPOIESIS

The data in the preceding review suggested strongly that the altered gastric secretions of patients with pernicious anemia has some profound effect on erythropoiesis. That achlorhydria alone is not responsible is evident because hydrochloric acid is useless in the treatment for pernicious anemia. It is futile to review the various theories whereby a gastro-intestinal sepsis was supposed to be induced by the absence of hydrochloric acid thus producing the anemia, because since the fundamental work of Castle and Sturgis and Isaacs [65] these theories may be discarded. Castle showed that the incubation of normal gastric juice on beef muscle produced a substance that brought about a remission in patients with pernicious anemia precisely comparable to that produced by liver therapy. By well controlled experiments, he showed that neither the hydrochloric acid alone nor the beef muscle alone, or both administered separately had any effect on the disease. It seems that this proof establishes the fact that the achlorhydria alone is not the cause for the absence of erythropoiesis, but that it represents the dominant indication of the specifically altered gastric secretion in pernicious anemia. Castle's work suggested that some unknown substance in normal gastric secretion might be the erythropoietic factor, whereupon Sturgis and Isaacs [65] prepared a dry extract from the normal stomach of a hog which, when given to patients with pernicious anemia, produced a characteristic response in the reticulocytes and a remission comparable to that obtained by liver therapy.

It would be hazardous at present to venture any theory as to the cause of pernicious anemia. The work that has been done in the past few years in America is portent with many possibilities. All that one can say at present is that pernicious anemia is partly the result of a deficiency and partly of a defective gastric hormone, of which achlorhydria is the most tangible sympton.

## SUMMARY AND CONCLUSIONS

1. Achlorhydria is such a constant sign in pernicious anemia that probably no case is valid unless achlorhydria is present.

2. Achlorhydria is not the result of the disease but is primary. Evidence for this is shown in the fact that there is no diminution of hydrochloric acid in the progress of a case of pernicious anemia and that achlorhydria is present from the onset, that achlorhydria persists in the stage of remission and that it has been found frequently for years before pernicious anemia became manifest.

65. Sturgis, C. C., and Isaacs, R.: Desiccated Stomach in the Treatment of Pernicious Anemia, J. A. M. A. **93**:747 (Sept. 7) 1929.

3. Achlorhydria occurs normally in a small percentage of persons. In order to determine this percentage, it is essential that mass studies be made with not only the fractional method of testing gastric secretion, but the tests with neutral red and histamine as well. The percentage of persons with achlorhydria apparently increases with each decade. It is extremely rare in childhood.

4. Achlorhydria is often present in certain families. In families in which a case of pernicious anemia has occurred, the incidence of achlorhydria is much higher than normal. As this incidence increases in each decade and as achlorhydria is exceptional in childhood, achlorhydria itself is not transmitted but only the tendency thereto.

5. Pernicious anemia is frequently hereditary and familial. Whether pernicious anemia is always hereditary and whether it is a dominant or recessive character and transmissible according to the mendelian law cannot be determined until such families are studied with particular reference to achlorhydria and with accurate hematologic examinations being made for three generations at least.

6. The available evidence is not convincing that *Bothriocephalus latus* causes pernicious anemia. There is ground for believing that such reported cases represent instances of true pernicious anemia that happen to be associated with infestation with *Bothriocephalus*.

7. There is a definite relation between achlorhydria and anemia of the pernicious, secondary and chlorotic types. The blood of relatives of patients with pernicious anemia shows changes, which sometimes may be regarded as the earliest or preclinical evidence of the disease. For diagnostic purposes, it is important to recognize this preclinical phase.

8. The development of pernicious anemia after an acquired achlorhydria, for instance after complete gastric resection, has not definitely been proved.

9. Many of the so-called "severe anemias" of pregnancy (exclusive of those due to hemorrhage or sepsis) represent cases of true pernicious anemia in which the patients have become pregnant. Whether the pregnancy is the inciting factor in patients with a constitutional tendency remains to be proved.

10. The anemia of sprue is often associated with achlorhydria. It is not yet established how often achlorhydria is acquired or is a constitutional tendency in this disease.

11. Achlorhydria is the most tangible but not the only evidence of the constitutional background of pernicious anemia. In all probability pernicious anemia represents a combination of a deficiency disease and a lack of a gastric hormone.

# CIRCULATION IN ARTERIOVENOUS ANEURYSM

## BEFORE AND AFTER OPERATION *

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An arteriovenous fistula in the human being offers an excellent opportunity to study the mechanics of the circulation under normal and abnormal conditions in the same person. It is one of the few diseases of the cardiovascular system that can be altered completely and permanently by an operative procedure. A physiologic study of the circulation in patients with an arteriovenous fistula is of interest, not only because of the phenomenal changes that sometimes occur, but because it affords an opportunity for a more complete understanding of other diseases of the cardiovascular mechanism.

These observations were undertaken in an attempt to determine the physiologic effect produced on the circulation by a large fistulous communication of six years' duration between the deep femoral artery and vein. The circulation was studied before and after obliteration of the fistula by operation. The secondary effects of this long-standing communication were quite marked; the heart was greatly enlarged, there was considerable sclerosis of the small vessels, and there had been two periods of congestive heart failure.

### REVIEW OF THE LITERATURE

During the past ten years, much experimental work has been done in an effort to explain the abnormal physiology of this condition. Detailed studies of the circulation in the dog have been made before and after experimental production of an arteriovenous fistula. Harrison, Dock and Holman [1] found that the cardiac output of the dog was approximately doubled following the production of an arteriovenous fistula, and that closure of the fistula resulted in a 48 per cent decrease in the circulatory minute volume. They believed that the cardiac hypertrophy associated with arteriovenous aneurysms was due to an actual increase in the amount of work done by the heart and to an

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* From the Medical and Surgical Clinics of the Emory University Division of the Grady Hospital.

1. Harrison, T. R.; Dock, W., and Holman, Emile: Experimental Studies in Arteriovenous Fistulae: Cardiac Output, Heart **11**:337, 1924.

increase in the total volume of blood. Holman [2] showed that the formation of an arteriovenous fistula is followed by an acceleration of the heart rate and a fall in blood pressure. He also pointed out that excision of the fistula caused a temporary increase in both systolic and diastolic blood pressures with a gradual adjustment to a more normal systolic level and a resultant decrease in pulse pressure. Holman [3] observed also that atropine prevents retardation in the heart rate when the fistula is closed. He concluded that the slowing of the heart rate was probably due to vagal stimulation, which occurs when the fistula is obliterated by compression and the increased blood pressure and blood volume distend the aorta. These studies did much to explain the observations made by Branham [3] in 1890 that obliteration of the thrill over an arteriovenous fistula by manual compression produced a marked slowing of the heart rate. Lewis and Drury [4] found a normal venous pressure and a decrease in the flow of blood through the arms and skin in certain patients with an arteriovenous anastomosis. They thought that the cardiac hypertrophy which occurs in this condition was due to a deficient coronary blood supply. They showed, however, that a rise in venous pressure and cardiac output occurred when the anastomosis was quite large. Since these observations were made, Holman [5] has demonstrated that the degree of change in the general circulation of patients with an arteriovenous aneurysm is dependent on the size and duration of the fistula.

Ellis and Weiss [6] lately reported studies of the circulation of two patients with recently acquired arteriovenous anastomosis. The communication in one of their patients was 3 mm. in diameter and produced the classic signs of an arteriovenous fistula. No similar studies of a patient with a large fistula of long standing and advanced general circulatory changes have been reported.

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2. Holman, Emile: The Physiology of an Arteriovenous Fistula, Arch. Surg. **7**:64 (July) 1923.

3. Branham, Harris H.: An Aneurism of the Femoral Artery Presenting a Strange and Unaccountable Phenomenon, Internat. J. Surg. **2**:250, 1890.

4. Lewis, T., and Drury, A. N.: Observations Relating to Arteriovenous Aneurism: 1. Circulatory Manifestations in Clinical Cases with Particular Reference to the Arterial Phenomena of Aortic Regurgitation, Heart **10**:301, 1923; 2. The Immediate Effects of an Arteriovenous Anastomosis on the Dog's Circulation, ibid., p. 365.

5. Holman, Emile: Experimental Studies in Arteriovenous Fistulae, Arch. Surg. **9**:822 (Nov.) 1924.

6. Ellis, Laurence B., and Weiss, Soma: The Local and Systemic Effects of Arteriovenous Fistula on the Circulation in Man, Am. Heart J. **5**:635, 1930.

## METHOD

Following the method of Field, Bock, Gildea and Lathrop,[7] twenty-three observations were made over a period of three months. These observations are divided as follows:

(1) First period: Preoperative, patient resting in bed (six observations).

(2) Second period: Thirteen days immediately after operation, patient resting in bed (six observations).

(3) Third period: Two months after operation (eleven observations). Recommunication of the fistula occurred during this time.

From these studies the following values were derived: the cardiac output per minute and per beat, the carbon dioxide content of arterial and venous blood, the carbon dioxide transport per hundred cubic centimeters of blood or the arteriovenous difference of carbon dioxide, the respiratory minute volume, the carbon dioxide excretion per minute, respiratory rate, percentage of oxygen and carbon dioxide of the expired air, and the basal metabolism. All observations were made in the basal state with the patient in a semi-upright position.

## RESULTS

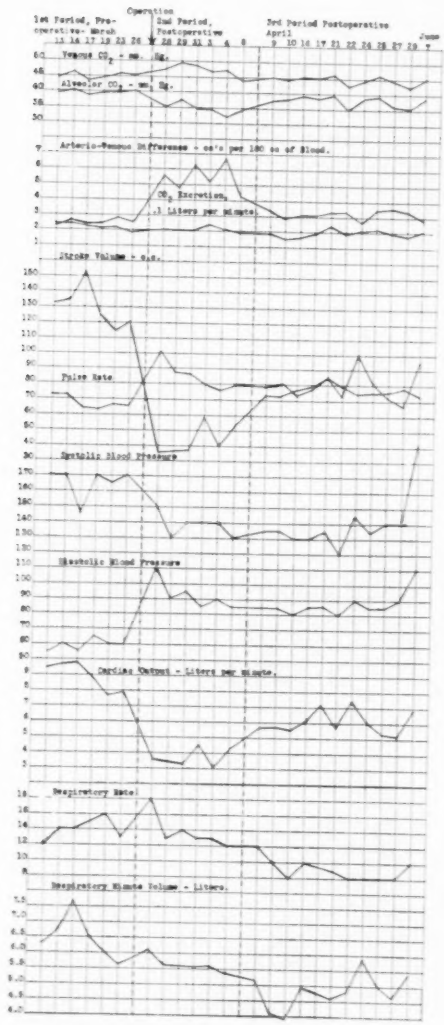
*Cardiac Output.*—Six observations made before operation ranged between 9.8 liters a minute with a stroke volume of 154 cc. and 7.7 liters a minute with a stroke volume of 115 cc. The average of these observations was 8.95 liters a minute and 131 cc. a beat.

Studies were resumed the second day after operation and six observations were made during the second period or next thirteen days. A striking decrease occurred in the cardiac output from a preoperative level of 8.95 to 3.76 liters a minute, a reduction of 58 per cent. There was a corresponding drop in stroke volume from 131 to 45 cc., or 65 per cent. The second day after operation a light bruit could be heard over a small area medial to the incision. The bruit remained constant in its intensity during this period of study. No thrill was palpable.

In the third period of study, eleven observations were made over an interval of two months. During this period the bruit became more intense, and at the time of the last observation a definite thrill was felt over the area of incision. Obliteration of the thrill by manual pressure did not change the heart rate or blood pressure.

The average cardiac output in the third period of study was 6.77 liters a minute, an increase of 44 per cent over the immediate postoperative cardiac output of 3.76 liters a minute observed during the second period. The stroke volume increased from 45 to 75 cc., or 75 per cent. These observations paralleled the physical signs of the reestablishment of the arteriovenous communication.

7. Field, J. H.; Bock, A. V.; Gildea, E. F., and Lathrop, F. L.: The Rate of the Circulation of the Blood in Normal Resting Individuals, J. Clin. Investigation **1**:65, 1924.




Graphic representation of the changes observed before and after operation.

TABLE I.—*All Observations Made Over the Entire Period of Study*

| Date, 1930 | Alveolar Percentage of Carbon Dioxide, Mm. Hg | Venous Percentage of Carbon Dioxide, Mm. Hg | Arteriovenous Difference in Percentage of Carbon Dioxide, per Cent by Volume | Carbon Dioxide Expired per Min., Cc. | Cardiac Output, Liters per Minute | Pulse Rate per Minute | Stroke Volume, Cc. | Blood Pressure | | Pulse Pressure | Oxygen Consumption per Minute, Cc. | Respiratory Quotient | Percentage of Oxygen Utilization of Inspired Air | Percentage of Carbon Dioxide Excretion of Expired Air | Respirations per Minute | Ventilation Liters per Minute | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Systolic Mm. Hg | Diastolic Mm. Hg | | | | | | | | |
| March 13 | 39.2 | 44.8 | 2.21 | 233 | 9.50 | 72 | 132 | 170 | 55 | 115 | 270 | 0.86 | 4.42 | 3.80 | 12 | 6.29 | Before operation |
| March 14 | 40.5 | 46.9 | 2.62 | 255 | 9.74 | 72 | 135 | 170 | 60 | 110 | 301 | 0.85 | 4.46 | 3.79 | 14 | 6.76 | Before operation |
| March 17 | 37.9 | 43.4 | 2.30 | 227 | 9.85 | 64 | 154 | 145 | 55 | 90 | ... | .... | .... | .... | 14 | 7.70 | Before operation |
| March 19 | 39.3 | 44.9 | 2.35 | 211 | 8.95 | 63 | 126 | 170 | 65 | 105 | 200 | 1.04 | 3.00 | 3.14 | 15 | 6.66 | Before operation |
| March 23 | 39.6 | 46.4 | 2.85 | 219 | 7.70 | 67 | 115 | 165 | 60 | 105 | 244 | 0.89 | 3.98 | 3.56 | 16 | 6.14 | Before operation |
| March 26 | 40.5 | 46.3 | 2.48 | 198 | 7.98 | 66 | 121 | 170 | 60 | 110 | 244 | 0.77 | 4.55 | 3.48 | 13 | 5.69 | Before operation |
| March 28 | 35.4 | 47.8 | 5.60 | 205 | 3.66 | 101 | 36 | 150 | 110 | 40 | 277 | 0.74 | 4.53 | 3.35 | 18 | 6.10 | 2 days after operation |
| March 29 | 37.8 | 49.6 | 4.75 | ... | .... | 87 | .. | 130 | 90 | 40 | ... | .... | .... | .... | 13 | .... | 3 days after operation |
| March 31 | 34.9 | 48.3 | 6.30 | 201 | 3.20 | 86 | 37 | 140 | 95 | 45 | 275 | 0.73 | 4.89 | 3.57 | 14 | 5.61 | 5 days after operation |
| April 3 | 34.5 | 46.2 | 5.26 | 246 | 4.67 | 79 | 59 | 140 | 85 | 55 | 245 | 0.83 | 4.28 | 3.56 | 13 | 5.52 | 8 days after operation |
| April 4 | 32.0 | 47.1 | 6.71 | 206 | 3.07 | 76 | 40 | 140 | 90 | 50 | 260 | 0.79 | 4.65 | 3.69 | 13 | 5.59 | 10 days after operation |
| April 8 | 34.2 | 44.0 | 4.37 | 185 | 4.23 | 79 | 54 | 130 | 85 | 45 | 215 | 0.86 | 3.95 | 3.39 | 12 | 5.44 | 14 days after operation |
| April 9 | 37.5 | 45.3 | 3.43 | 196 | 5.72 | 78 | 73 | 135 | 85 | 50 | 236 | 0.83 | 4.16 | 3.45 | 12 | 5.67 | 15 days after operation |
| April 10 | 37.7 | 44.4 | 2.91 | 166 | 5.72 | 80 | 72 | 135 | 85 | 50 | 206 | 0.81 | 4.42 | 3.57 | 10 | 4.66 | 16 days after operation |
| April 16 | 38.7 | 45.8 | 3.10 | 172 | 5.55 | 72 | 77 | 130 | 80 | 50 | 206 | 0.83 | 4.66 | 3.80 | 8 | 4.41 | 22 days after operation |
| April 17 | 37.9 | 45.0 | 3.10 | 190 | 6.13 | 78 | 79 | 130 | 85 | 45 | 234 | 0.81 | 4.28 | 3.46 | 10 | 5.48 | 23 days after operation |
| April 21 | 39.0 | 46.9 | 3.30 | 238 | 7.20 | 84 | 86 | 135 | 85 | 50 | ... | .... | .... | .... | .. | .... | 27 days after operation |
| April 22 | 35.0 | 42.7 | 3.38 | 194 | 5.74 | 79 | 73 | 120 | 80 | 40 | 236 | 0.82 | 4.59 | 3.77 | 9 | 5.15 | 28 days after operation |
| April 24 | 38.3 | 44.6 | 2.72 | 202 | 7.40 | 74 | 100 | 145 | 90 | 55 | 233 | 0.87 | 4.39 | 3.80 | 8 | 5.31 | 30 days after operation |
| April 25 | 38.7 | 46.5 | 3.47 | 210 | 6.05 | 75 | 81 | 135 | 85 | 50 | 232 | 0.91 | 3.92 | 3.55 | 8 | 5.91 | 31 days after operation |
| April 27 | 35.9 | 44.1 | 3.62 | 196 | 5.42 | 75 | 72 | 140 | 85 | 55 | 221 | 0.89 | 4.35 | 3.86 | 8 | 5.08 | 33 days after operation |
| April 29 | 35.2 | 42.2 | 3.38 | 176 | 5.21 | 78 | 67 | 140 | 90 | 50 | 213 | 0.82 | 4.55 | 3.75 | 8 | 4.69 | 35 days after operation |
| June 7 | 38.4 | 45.2 | 2.89 | 201 | 6.96 | 73 | 95 | 195 | 110 | 95 | 275 | 0.73 | 5.11 | 3.72 | 10 | 5.40 | 10 weeks after operation |

*Blood Pressure.*—Before operation, the average blood pressure was 164 mm. systolic and 59 mm. diastolic, with a pulse pressure of 105 mm. Following operation, there was a drop of 16 per cent in the systolic pressure to 138 mm., while the diastolic pressure increased 56 per cent to 92 mm., a change in percentage almost equal to the decrease which occurred in the cardiac output. During the next ten observations, made over a period of one month while the patient was in the hospital, the blood pressure remained unchanged. After the patient was discharged from the hospital, the blood pressure increased to 195 mm. systolic and 110 mm. diastolic. Because of the sustained elevation of the diastolic pressure, it was thought that this change in blood pressure was a result of the coexistent arteriosclerosis and hypertension rather than of any change which occurred in the arteriovenous communication.

Thus it seems that the reestablishment of the fistulous communication did not cause any significant change in blood pressure even though there was an increase in the cardiac output. An explanation of this is not clear, but it confirms observations made previously [8] that very little relation exists between blood pressure and cardiac output, even in the same person.

*Heart Rate.*—Obliteration of the fistula by manual compression resulted in a 20 per cent decrease in the heart rate from 100 to 80 beats a minute. This decrease was accompanied by a considerable rise in both systolic and diastolic blood pressures.

The average heart rate before operation was 67 beats a minute. During the immediate postoperative period, the heart rate increased from 67 to 85 beats a minute, or 27 per cent. This increased rate was maintained throughout the remainder of the study, although there was a tendency for some decrease to occur as the fistulous communication became reestablished. These results are not in accord with those of Ellis and Weiss,[6] who found a decrease in heart rate both when the fistula was temporarily closed by manual pressure and also following permanent closure by operation.

*Vital Capacity.*—There was a gradual increase in the vital capacity from 2.4 to 4.1 liters extending over the entire period of observation. This increase was not directly related to any immediate change in the circulatory mechanism resulting from obliteration of the fistula but was probably due to improved circulatory efficiency, the result of prolonged rest in bed and closure of the fistula.

8. Burwell, C. Sidney; and Smith, Carter: The Output of the Heart in Patients with Abnormal Blood Pressures, J. Clin. Investigation **7**:1, 1929.

*Respiratory Rate and Minute Volume.*—The average respiratory rates during the first and second periods of study were 14 a minute. During the third period, the respiratory rate decreased to 9 a minute.

The respiratory minute volume was 6.54 liters before operation, 5.04 liters during the second period, and 4.97 liters during the third period or last two months of observation. Here again, the gradual decrease in respiratory minute volume was probably related to a general increase in circulatory efficiency rather than to any immediate alteration of the circulation by obliteration of the fistula.

*Per Cent of Oxygen Utilization and Carbon Dioxide Excretion of the Expired Air.*—Coincident with the decrease in respiratory rate and minute volume there was an increase of 9.3 per cent in the amount of oxygen utilized from the inspired air and an increase of 3.6 per cent in the carbon dioxide content of the expired air. This same phenomenon occurs in patients recovering from cardiac failure,[9] but is then accompanied by an increase in the carbon dioxide content of alveolar air. In this patient the alveolar air showed a decrease in the carbon dioxide content.

*Oxygen Consumption and Carbon Dioxide Excretion.*—There was a gradual decrease in the patient's metabolic rate during his stay in the hospital. The oxygen consumption decreased 11 per cent and the carbon dioxide excretion 14 per cent. This was probably the result of prolonged rest in bed, as observations made after the patient was discharged from the hospital showed an increase in oxygen consumption to the level obtained when the patient was first observed.

*Carbon Dioxide Tension of Arterial and Venous Blood.*—The carbon dioxide tension of the arterial blood estimated from alveolar air showed an average preoperative level of 39.5 mm. of mercury. Immediately following operation it fell to an average of 34.8 mm. of mercury, a decrease of 12 per cent. During the third period of study there was an abrupt rise to 37.5 mm. of mercury, an increase of 7.7 per cent. This increased level of carbon dioxide tension in the arterial blood was maintained throughout the remainder of the study and was interpreted as one of the earliest and most definite signs of a recommunication of the arteriovenous communication.

There was an average carbon dioxide tension of 45.5 mm. of mercury in the venous blood before operation. Following operation during the second period of study, there was an average increase to 47.1 mm.

9. Peters, J. P., Jr., and Barr, D. P.: Studies of the Respiratory Mechanism in Cardiac Dyspnea: 1. Low Alveolar Carbon Dioxide of Cardiac Dyspnea, Am. J. Physiol. **54**:307, 1920; 2. Effective Ventilation in Cardiac Dyspnea, ibid., p. 345.

of mercury, or 3.5 per cent, a much smaller change than that which occurred in the arterial level of carbon dioxide tension. During the third period of study when a recommunication of the fistula occurred, there was an increase to 44.8 mm. of mercury, or 4.7 per cent. This was quite similar to the level of carbon dioxide in the venous blood before operation.

*Carbon Dioxide Transport.*—The amount of carbon dioxide given off in the lungs by 100 cc. of blood was 2.47 per cent by volume before the operation. Immediately following operation or during the second period of study, there was an average increase to 5.49 per cent by volume, or a change of 122 per cent. Interpreted in terms of oxygen transport or the coefficient of utilization, this represents a remarkable increase in circulatory efficiency. More than twice as much oxygen was being utilized from 100 cc. of blood, and the tissue supply of oxygen was adequate, even though there was a decrease of 58 per cent in the cardiac output.

As the arteriovenous fistula became reestablished, there was a decrease in the carbon dioxide transport to 3.21 per cent by volume, a reduction of 42 per cent. This decrease in the coefficient of utilization was accompanied by an increase of 44 per cent in the cardiac output and represented a great decrease in circulatory efficiency.

The variations in the arteriovenous difference of carbon dioxide (carbon dioxide transport) that accompanied the changes in cardiac output were represented largely by fluctuations in the arterial level of this gas, while the venous carbon dioxide remained relatively constant. This is in accord with observations made previously [10] that pathologic variations in the circulatory minute volume show the change in the carbon dioxide transport to be represented largely by a fluctuation in the arterial level of this gas. In physiologic variations of the cardiac output, as produced by exercise, for example, the change in the carbon dioxide transport is represented largely by a change in the venous level of this gas, while the arterial level remains quite constant.

## COMMENT

The results of this study show that an arteriovenous fistula can greatly impair the efficiency of the circulation by causing an increase in the cardiac output and a decrease in the coefficient of utilization. This

10. Smith, W. C.; Walker, G. L., and Alt, H. L.: The Cardiac Output in Heart Disease: 1. Complete Heart Block, Auricular Fibrillation before and after the Restoration to Normal Rhythm, Subacute Rheumatic Fever and Chronic Rheumatic Valvular Disease, Arch. Int. Med. **45**:706 (May) 1930; 2. Effect of Exercise on the Circulation in Patients with Chronic Rheumatic Valvular Disease, Subacute Rheumatic Fever and Complete Heart Block, ibid. **45**:958 (June) 1930.

TABLE 2.—*The Averages in Preoperative and Postoperative Observations*

| Date | Number of Observations | Alveolar Percentage of Carbon Dioxide, Mm. Hg | Venous Percentage of Carbon Dioxide, Mm. Hg | Arteriovenous Difference in Percentage of Carbon Dioxide, % by Volume | Carbon Dioxide Expired per Minute, Cc. | Cardiac Output, Liters per Minute | Pulse Rate per Minute | Stroke Volume, Cc. | Blood Pressure | | Pulse Pressure | Oxygen Consumption per Minute, Cc. | Respiratory Quotient | Percentage of Oxygen Utilization of Inspired Air | Percentage of Carbon Dioxide Excretion of Expired Air | Respirations per Minute | Ventilation, Liters per Minute | Vital Capacity, Liters |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Systolic, Mm. Hg | Diastolic, Mm. Hg | | | | | | | | |
| 13 days before operation | 6 | 39.5 | 45.5 | 2.47 | 224 | 8.95 | 67 | 131 | 164 | 59 | 105 | 254 | 0.88 | 4.08 | 3.55 | 14 | 6.54 | 3.3 |
| First 13 days after operation | 6 | 34.8 | 47.1 | 5.49 | 208 | 3.76 | 85 | 45 | 138 | 92 | 46 | 254 | 0.81 | 4.46 | 3.57 | 14 | 5.65 | 3.5 |
| Next 2 months after operation | 11 | 37.5 | 44.8 | 3.21 | 195 | 6.77 | 77 | 79 | 139 | 88 | 56 | 296 | 0.84 | 4.44 | 3.68 | 9 | 4.97 | 3.99 |

fact has previously been demonstrated in experimental animals by Holman and others. That cardiac failure may be a result of this decreased circulatory efficiency is also well known.

The studies recently reported by Ellis and Weiss[6] illustrate the immediate effects of a recently acquired arteriovenous fistula on the circulation. The observations reported in this paper show the secondary circulatory effects of a fistula of long standing. A comparison of these two studies is of interest.

The arteriovenous fistula in the patient treated by Ellis and Weiss was 3 mm. in width and produced the classic signs of this condition, i. e., increased pulse pressure, increased heart rate and Branham's phenomenon. The communication was, however, of only one month's duration, and there was no evident peripheral vascular damage. No change occurred in the cardiac output before or after operation.

In my patient there was a demonstrable reduction of 58 per cent in the cardiac output following operative closure of the fistula. The arteriovenous communication was of six years' duration, the peripheral vascular damage was marked and two periods of congestive heart failure had occurred.

The difference in my results and those of Ellis and Weiss are possibly due to the duration of the arteriovenous fistula and the resulting peripheral vascular changes.

It seems that in some instances, as shown by Ellis and Weiss, even though the communication is quite large, the peripheral vascular bed is capable of adjusting the circulation so that normal efficiency is still maintained. This circulatory adjustment of the capillary bed is probably a centrally controlled function. With the occurrence of general damage to the peripheral vascular bed, as demonstrated by my patient, this compensatory function is lost, the cardiac output increases and there is a decrease in circulatory efficiency.

## SUMMARY

A measure of the cardiac output and related values was undertaken before and after operation in a person with a large arteriovenous communication of six years' duration and with secondary cardiovascular changes.

A reduction of 58 per cent in cardiac output and an increase of 122 per cent in the coefficient of utilization occurred following operative closure of the fistula. There was a gradual recommunication of the fistula after operation. This resulted in an increase in the cardiac output and a decrease in the coefficient of utilization.

REPORT OF A CASE

*History.*—M. H., a colored male laborer, aged 40 years, was admitted to the Emory University Division of the Grady Hospital on Feb. 2, 1930, and discharged on April 17, 1930. Six years before admission to the hospital he was shot through the left groin with a pistol. He was sent to a hospital at that time and remained there six weeks. When discharged, he was told that he had an arteriovenous aneurysm. Four weeks after discharge, he began to experience shortness of breath and swelling of the feet and legs. This became so severe that he was forced to seek readmission to the hospital, where he remained for eight weeks. He was discharged feeling quite well. The Wassermann reaction of the blood was strongly positive at that time and he was given antisyphilitic treatment as long as he remained in the hospital.

He was able to work for one year and a half as a laborer; then the symptoms of cardiac failure returned, and he was readmitted to the hospital for a period of five weeks. At the end of this time, he returned to work and was free from symptom for about three and a half years.

He was first seen in this clinic in January, 1930. At this time he had a moderate degree of cardiac failure for which he was treated. He failed to respond to treatment, however, and was admitted to the hospital the next month.

There was a history of a penile lesion in 1918. He received only local treatment at that time.

*Physical Examination.*—The patient was moderately dyspneic and orthopneic. There was no detectable cyanosis. Ophthalmoscopic examination showed normal disks, but the retinal arteries were moderately sclerosed. The jugular veins were moderately distended and there was visible pulsation of the great vessels of the neck. The respiratory rate was 22 per minute; the lungs were clear except for a few medium moist râles at the bases posteriorly. The heart was greatly enlarged. The apex impulse was diffuse and heaving in the fourth, fifth and sixth interspaces extending out into the anterior axillary line. The cardiac dulness was 13.5 cm. to the left, 5 cm. to the right with a supracardiac dulness of 6 cm. The first sound at the apex was accentuated and partially replaced by a systolic murmur. There was a gallop rhythm at a rate of 120 beats a minute. The aortic second sound was accentuated and of impure quality. The radial vessels were moderately sclerosed. The blood pressures were as follows: right arm, 200 mm. systolic and 90 mm. diastolic; left arm, 210 mm. systolic and 90 mm. diastolic; right leg, 270 mm. systolic and 90 mm. diastolic; left leg, 160 mm. systolic and 50 mm. diastolic.

Following manual compression and obliteration of the fistula in the left femoral region, the blood pressure in the right arm increased to 240 mm. systolic and 100 mm. diastolic. This increase was maintained for about four minutes and then began to return to its previous level. There was a simultaneous slowing of the heart rate from 100 to 80 a minute.

The abdomen was moderately distended, the liver could be felt 6 cm. below the costal border. There was a small amount of free fluid in the abdomen.

In the left inguinal region there was a small pulsating mass about 3 cm. in width and 6 cm. in length. There was a continuous thrill and bruit over this mass, which could be obliterated by manual pressure.

There was moderate pitting edema of both legs. The superficial veins around the arteriovenous anastomosis were dilated, and there was a definite increase in the skin temperature of that area. Dorsalis pedis pulsations were easily felt in both feet.

*Laboratory Examinations.*—The urinalysis was negative; the blood count was normal both before and after operation. The blood chemistry was normal, but the Wassermann reaction of the blood was strongly positive. A teleoroentgenogram at the time of admission showed an aortic shadow of 5 cm.; the left margin was 13 cm., the right margin 5 cm., with a transverse thoracic diameter of 28 cm. A second plate made one month after operation showed a definite decrease in the heart shadow. The measurements at that time were 11.5 cm. to the left, 4.5 cm. to the right; the aortic shadow was 6 cm. and the transverse diameter of the chest, 29 cm.

*Clinical Course.*—The patient was given digitalis and antisyphilitic treatment by mouth. There was a rapid subsidence of the edema and of the shortness of breath. By the end of the first week in the hospital he was free from edema and could lie flat in bed without discomfort. The vital capacity had increased from 2.4 to 3.1 liters. The blood pressure was 160 mm. systolic and 80 mm. diastolic.

Two weeks after admission, the patient was well compensated. The lungs were clear throughout, and there was no peripheral edema. The vital capacity was 3.4 liters, respirations were 12 a minute, the heart rate was 72 a minute and the blood pressure was 170 mm. systolic and 55 mm. diastolic. Studies of the cardiac output and related values were begun at this time.

Four weeks after the patient was admitted to the hospital, Dr. J. L. Campbell performed a quadruple ligation of the femoral and deep femoral arteries and veins. It was impossible to isolate the direct communication between the artery and vein, and its actual size could not be determined. There was considerable dilatation of the adjacent veins.

The day after operation, the patient's general condition was good. There was no difference in the skin temperature of the legs. The blood pressure was 195 mm. systolic and 115 mm. diastolic. The heart rate was 80 a minute with an occasional premature beat. No thrill or bruit was found over the site of operation. The second day after operation, the patient was able to sit up in bed. A measure of the cardiac output was done in this position. The fourth day after operation, a faint bruit but no thrill was detected over a small area medial to the incision. This bruit could be heard over a wider area and was more intense during the remainder of his stay in the hospital. The patient remained in bed three weeks, and repeated observations of the cardiac output were made during this time. He was discharged nine weeks after admission and was not seen again for seven weeks. At this time a definite thrill and bruit were found over the left femoral region. These could be obliterated by pressure, but there was no change in the heart rate or blood pressure. He was free from symptoms, and the vital capacity was 4.1 liters. Observations of the cardiac output were repeated at this time. He was seen again five months later. The physical signs were unchanged, and he was capable of performing light work without discomfort.

# MALIGNANT NEPHROSCLEROSIS

## PATHOGENESIS *

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In primary arterial hypertension the essential renal lesion is nephrosclerosis. In most cases, the nephrosclerosis is in itself benign. The chronic hypertension terminates in cardiac insufficiency, in a cerebrovascular accident, in a coronary accident or through some incidental cause. In the remaining cases, the nephrosclerosis itself is the malignant, lethal factor, and the hypertensive state is closed by uremia.

In most cases the clinical and morphologic distinction between benign and malignant nephrosclerosis is sharp. The group of chronic hypertensions that ends through some factor other than renal insufficiency almost always presents the well defined histologic picture of simple renal arteriosclerosis. The group that ends in uremia is usually associated with a marked and abrupt, but just as well defined, change in the histologic picture. Transitions are scanty, and so striking are the morphologic differences that in their original presentation of the subject, Volhard and Fahr [1] postulated the addition of an altogether different etiology and pathogenesis for the malignant form. They regarded the new histologic changes as inflammatory rather than sclerotic. They conceived that benign nephrosclerosis turned into a malignant form and ended in uremia, when a toxic-irritative or inflammatory factor was imposed on the predisposing arteriolosclerosis.

The existence of such an inflammatory-sclerotic combination form was hotly contested by other investigators. Löhlein,[2] in particular, firmly insisted that malignant nephrosclerosis was but another form of benign sclerosis; both conditions were arteriolosclerotic, the same in etiology and in pathogenesis and differed only in the "tempo" of development. As far as renal function was concerned, slow arteriosclerosis of the kidneys was benign. The slow decrease in the glomerular blood supply led to the characteristic hyaline and atrophic changes.

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* From the Department of Pathology, Cook County Hospital.

1. Volhard, F., and Fahr, T.: Die Brightsche Nierenkrankheit, Berlin, Julius Springer, 1914.

2. Löhlein, M.: Ueber Schrumpfnieren, Beitr. z. path. Anat. u. z. allg. Path. **63**:570, 1917; Zur Nephrocirrhosis arteriolosclerotica, Med. Klin. **14**:136, 1918; Zur vasculären Nierensklerose, ibid. **12**:1042, 1916; Zur Pathogenese der vasculären Schrumpfniere, ibid. **12**:741 and 872, 1916; Erwiderung auf T. Fahr's Aufsatz, Zentralbl. f. Path. u. path. Anat. **28**:209, 1916.

but did not appreciably impair renal function. Similar but more rapidly developing arteriolosclerosis brought with it an abrupt glomerular ischemia, which led to more intense histologic changes and to death in uremia. The process was the same, only faster, and no new toxic factor had to be invoked.

Jores,[3] too, believed that there was no fundamental difference between the two forms. He emphasized the diffuse involvement of the finest vessels in malignant nephrosclerosis as compared with the focal involvement and the predominant sclerosis of the larger vessels in the benign form. Fishberg,[4] Stern,[5] Murphy and Grill [6] and the majority of authors agreed with Löhlein that both forms were sclerotic. In the malignant form there was no added inflammatory factor, but only an acceleration of the same sclerosis. In a recent, extensive study of 420 cases of primary arterial hypertension, including 36 cases of death in uremia, Bell and Clawson [7] pointed out that when the uremia had developed slowly, the renal changes were those of simple sclerotic atrophy. They found that rapidly developing uremias were associated with the more severe changes of malignant nephrosclerosis. They ascribed these changes only to more abrupt arterial occlusion and not to any added toxic factor.

Meyer,[8] Sternberg,[9] Ask-Upmark [10] and others, however, could never reconcile themselves to the view that the changes in malignant nephrosclerosis were merely sclerotic.

The malignant forms were found especially in younger patients in whom there should be least sclerosis. The changes were so widely different from those of benign sclerosis, and they resembled the changes of focal nephritis and of periarteritis nodosa so closely, that it forced

3. Jores, L.: Ueber die Arteriosklerose der kleiner Organarterien und ihre Beziehungen zur Nephritis, Virchows Arch. f. path. Anat. **178**:367, 1904.

4. Fishberg, A. M.: Anatomic Findings in Essential Hypertension, Arch. Int. Med. **35**:650 (May) 1925; The Arteriolar Lesions of Glomerulo-Nephritis, ibid. **40**:80 (July) 1927.

5. Stern, M.: Ueber einen besonders akut verlaufenen Fall von Arteriolonekrose der Nieren, Virchows Arch. f. path. Anat. **251**:718, 1924.

6. Murphy, F., and Grill, J.: So-Called Malignant Hypertension: A Clinical and Morphologic Study, Arch. Int. Med. **46**:75 (July) 1930.

7. Bell, E. T., and Clawson, B. J.: Primary Hypertension, Arch. Path. **5**: 939 (June) 1928.

8. Meyer, O.: Ueber das Vorkommen und die Bedeutung entzuendlicher Gefässveränderungen in den Nieren, Verhandl. d. deutsch. path. Gesellsch. **19**: 352, 1923.

9. Sternberg, B.: Thrombo-Angionecrotic Changes of the Kidneys in Chronic Nephritis, Arch. Int. Med. **44**:272 (Aug.) 1929.

10. Ask-Upmark, E.: Ueber juvenile maligne Nephrosklerose und ihr Verhältnis zu Störungen in der Nierenentwicklung, Acta path. et microbiol. Scandinav. **6**:383, 1929.

the impression of a superimposed toxic element. Fahr, especially, maintained that sclerotic ischemia could never account for the proliferative and other changes seen in the malignant forms, and that an added inflammatory or toxic element would have to be accepted.[11]

In the long controversy that has been waged over the etiology and pathogenesis of malignant nephrosclerosis, numerous bitter polemics have been exchanged, an extensive literature has developed, and a large amount of critical observation and experimentation has been stimulated. Herxheimer[12] finally suggested in this argument that questions of etiology had not been sufficiently separated from those of pathogenesis. As long as nothing definite was known (and nothing definite is yet known) about the etiology of either the benign or the malignant forms, their etiologic separation or identification was only a matter of the subjective opinion of the individual investigator. So far, only their respective pathogeneses could be studied and compared, and questions of etiology should be avoided until something more definite was known. He agreed with Fahr in the recognition of the fact that aside from a high grade, slow arteriolosclerosis, there were other arteriolar changes that could lead much more rapidly to uremia. Herxheimer pointed out that these changes were different from those of benign sclerosis, but he did not believe them to be of inflammatory origin.

At first Volhard had been led to assume a toxic basis for the malignant changes, because of their resemblance to nephritis. But with his conception that the pathogenesis of nephritis was based on glomerular ischemia, he conceded that malignant nephrosclerosis might also be only ischemic in origin, an accelerated form of benign nephrosclerotic ischemia. He therefore relinquished his original position with Fahr on this subject. He attributed the onset of the renal insufficiency to a general and renal vasoconstriction, with abrupt glomerular capillary spasm. Severe glomerular ischemia led to the degenerative and reactive proliferative changes seen in the malignant forms.[13]

11. Fahr, T.: Ueber atypische Befunde aus den Kapiteln des Morbus Brightii nebst anhangsweisen Bemerkungen zur Hypertoniefrage, Virchows Arch. f. path. Anat. **248**:323, 1924; Pathologische Anatomie des Morbus Brightii, in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 6. Ueber Nephrosklerose, Virchows Arch. f. path. Anat. **226**:119, 1919; Ueber maligne Nierensklerose (Kombinationsform), Zentralbl. f. Path. u. path. Anat. **27**:481, 1916; Ueber die Beziehungen von Arteriolensklerose, Hypertonie und Herzhypertrophie, Virchows Arch. f. path. Anat. **239**:41, 1922; Kurze Bemerkungen zur Frage der malignen Nierensklerose, Zentralbl. f. Path. u. path. Anat. **28**:408, 1917.

12. Herxheimer, G.: Niere und Hypertonie, Verhandl. d. deutsch. path. Gesellsch. **15**:211, 1912; Ueber Arteriolonekrose der Nieren, Virchows Arch. f. path. Anat. **25**:709, 1924.

13. Volhard, F.: Der arterielle Hochdruck, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **35**:134, 1923.

It was objected that the cause of the glomerular ischemia could not lie in capillary spasm. Capillary spasm should produce the most marked ischemic changes distal to the glomerulus, whereas they were often seen only proximal to the glomerulus in the afferent arteriole and not in the glomerulus. The cause of the glomerular ischemia must therefore lie somewhere proximal to the glomerulus.

Klemperer and Otani were struck with the fact that glomerular changes identical with those of malignant nephrosclerosis could be found in the periphery of recent, aseptic, renal infarcts. They declared: "Here, there could be no doubt as to the ischemic nature of these changes." They maintained with Volhard that benign nephrosclerosis and malignant nephrosclerosis were essentially the same and that both were ischemic. But they traced the origin of the glomerular changes in the malignant form, not to capillary spasm, but to thrombotic or proliferative occlusion at some point in the corresponding afferent arterioles.[15] They demonstrated these occlusions by painstaking serial sections.

The uninjected kidney, however, is not altogether reliable material from which to study the vascular condition of that organ. Sjövall[16] fixed kidneys by the ordinary immersion in formaldehyde, as well as by injecting formaldehyde into the renal artery. He demonstrated great discrepancies between the histologic pictures of the injected and those of the uninjected specimens. Vessels that were apparently occluded by thrombi or proliferation in the uninjected specimens were widely patent in the injected ones. Gustav Ricker's observations, which were made directly on the living animal, also strongly emphasized that many of the histologic pictures that have been accepted as ischemic were only agonal or postmortem artefacts.[17]

In view of the foregoing investigations, a study was attempted of the nephrosclerotic material available from 1,000 consecutive autopsies performed at the Cook County Hospital on patients over 20 years of age. An injection method was used to check the direct observations. In the course of this study, certain histologic changes attracted attention, which amplified the transition between benign and malignant nephrosclerosis. Analyzed on the basis of Ricker's views, they identified the benign and malignant forms, whatever their respective etiologies

14. Reference deleted by author.

15. Klemperer, P., and Otani, S.: Studies on Malignant Nephrosclerosis, personal communication; Studies on Malignant Sclerosis of the Kidneys, Arch. Path. **8**:559 (Sept.) 1929.

16. Sjövall, E.: Ueber die anatomischen Formen der Nephrosclerose, Acta med. Scandinav. **65**:484, 1927.

17. Ricker, Gustav: Sklerose und Hypertonie der innervierten Arterien, Berlin, Julius Springer, 1927.

may have been, in a single pathogenesis. They offered for both a single hemodynamic mechanism, which, however, is not as commonly accepted ischemic, but which is a form of hyperemia with retardation.

## STATISTICAL STUDY

Among the 1,000 autopsies, there were altogether 171 cases of nephrosclerosis, 36 with uremia and 135 without uremia. In 47 per cent (80 cases) of the entire series, the chronic hypertension terminated in cardiac decompensation, in 9 per cent (16 cases) by a coronary accident, in 19 per cent (32 cases) by a cerebral vascular accident, in 4 per cent (7 cases) through some incidental cause and in 21 per cent (36 cases) in uremia.

In the large, extra-uremic, so-called "benign" group, eighty-six patients, or 64 per cent, were over 50 years of age and forty-nine patients, or 36 per cent, were under 50 years of age. Seventy-one per cent of Klemperer and Otani's patients were over 50. Forty-five cases, or 33 per cent, occurred in women, and ninety cases, or 67 per cent, in men. This ratio is practically the same as the relative proportion of autopsies performed on men and on women, 30 and 70 per cent, respectively, in the entire series. Therefore, men were affected as commonly as women.

Fifty (37 per cent) of the 135 cases occurred in colored patients, and 85 (63 per cent) in white patients. This percentage is exactly the same as that obtained at the Cook County Hospital in the entire series of 1,000 cases. Thus colored patients were affected as commonly as white. Therefore, there was no special sexual or racial predisposition toward benign nephrosclerosis. Forty-one cases (30 per cent) occurred in syphilitic patients, and 94 cases (70 per cent) occurred in nonsyphilitic patients. Judged by the characteristic changes in the aorta, of the entire 1,000 patients only 17 per cent were syphilitic. In the series of nephrosclerotic patients, 21, or 42 per cent, of the 50 colored patients were syphilitic. Nineteen, or 22 per cent, of the 85 white patients were syphilitic. This relative proportion is about the same as that for syphilis in colored and white patients (2:1) in the entire 1,000 autopsies. It can be concluded that as far as the material from the Cook County Hospital demonstrates, syphilis is almost twice as frequent in patients with benign nephrosclerosis as it is in those who do not have nephrosclerosis, and the importance of the syphilitic factor is the same in the colored as in the white patients.

Of the thirty-six patients who died of uremia, twenty-five, or 69 per cent, were less than 50 years of age, while eleven, or 21 per cent, were over 50. In Klemperer and Otani's patients, 75 per cent were under 50 years of age. This slight difference in percentage arises only

from the slightly different type of material which is included in the uremic series in this paper. With the same type of cases that Klemperer presented, the proportion of cases at the Cook County Hospital in which the patients were under 50 years of age is the same, 74 per cent. Klemperer and Otani found that the average age of women was 44 years; of men, 30. In this series, even when the results were corrected for the difference in the type of case, the average age for both men and women was the same, 46 years.

Twelve, or 33 per cent, of the uremic patients were syphilitic, twenty-four, or 67 per cent, were nonsyphilitic. This proportion was the same as that found in benign nephrosclerosis. Of these twelve patients, seven were colored and five were white; this too was about the same relative proportion as that found for syphilis in benign sclerosis. The syphilitic factor here too was the same in the colored patients as in the white ones. It could be concluded that syphilis predisposes to nephrosclerosis in general, but no more to the malignant form than to the benign.

Twenty-six, or 72.3 per cent, of the cases occurred in colored persons, and 10 cases, or 27.7 per cent, in white patients. Since in the entire 1,000 autopsies only 36.5 per cent occurred in colored patients, the incidence of nephrosclerosis with uremia was twice as frequent in the colored as in the white group. In benign nephrosclerosis, the incidence in both races was equal, for the racial proportion of cases was the same as in the entire 1,000 cases. Therefore, while there is no racial predisposition to benign nephrosclerosis, there is a distinct predisposition of the colored race to nephrosclerosis with uremia.

Seventeen, or 47 per cent, of the cases occurred in women; nineteen, or 53 per cent, in men. In the entire series, only 30 per cent occurred in women. Corrected for this general percentage, the proportion of men to women in malignant nephrosclerosis was 1 : 2.4, while in benign nephrosclerosis the proportion was 1 : 1. Therefore, there is a distinct predisposition of the female sex to malignant nephrosclerosis, while no such predisposition exists to the benign form.

### CLINICAL AND MORPHOLOGIC STUDY

Among the thirty-six cases of nephrosclerosis with uremia, in only one had the uremia been induced by simple progressive shrinking of the substance of the kidney until there was not enough of it left to support life (case 35, table 1). In this case practically every glomerulus was partly or completely hyalinized or was involved in pericapsular fibrosis.[18]

18. McGregor, L.: Histological Changes in the Renal Glomerulus in Essential Hypertension, Am. J. Path. **6**:347, 1929.

Hardly a normal glomerulus was found. This type of termination is rare, because the sclerosis is slow and because the nephrosclerotic patient is in a constant, precarious state from many other renal and extrarenal vascular dangers. Before the kidney shrinks to a point incompatible with life, the slow sclerotic process is usually stopped abruptly by cardiac failure, a cerebral vascular accident, a coronary accident or through some incidental cause. Long before marked renal atrophy has occurred, the prolonged strain of maintaining high blood pressure and the vascular changes in the myocardium sometimes lead to cardiac decompensation, which even of itself may not be fatal, but which precipitates uremia by abruptly aggravating the renal circulatory embarrassment.[19] There were four such cases in this series. In three (cases 33, 34 and 35) a moderate degree of renal atrophy had been reached. About 35 per cent of the glomeruli were partly or completely hyalinized; about 25 or 30 per cent were involved in pericapsular fibrosis and shrinking. The remaining 30 or 35 per cent were unchanged, except as they showed some degree of capillary dilatation. A marked degree of capillary dilatation was prominent in the intertubular capillaries of these kidneys, as a sign of the cardiac passive congestion that had precipitated the fatal renal insufficiency. In one case (case 36) the predisposing renal sclerosis had advanced but slightly when the kidneys were thrown out of function and uremia was precipitated by passive congestion.

The majority of the cases ending in uremia, thirty-one of thirty-six, did not show enough renal atrophy or enough passive congestion to account for the renal failure. The uremic issue was determined by an altogether different type of renal change. Twenty-three of the cases answered Fahr's classic description of malignant nephrosclerosis.

*Clinical Picture.*—The usual clinical picture was that of chronic hypertension of long duration in patients less than 50 years of age; the condition occurred in women more commonly than in men and in colored patients more commonly than in white ones. There was no history of previous nephritis. The patients had usually been robust and sturdy and often had engaged in hard manual labor until a short time before admission. In most cases the duration of the antecedent hypertensive phase could not be accurately determined. Some of the patients had known that they had had a high blood pressure for from six months to ten years; other patients were totally unaware of it until the time of admission. Whenever noted, the hypertension was almost always found to be constant and exceedingly high. Often the condition was symptomless; at other times it was associated with headaches, weakness, ner-

19. Baehr, G., and Ritter, S. A.: The Arterial Supply of the Kidney in Nephritis, Arch. Path. **7**:458 (March) 1929.

TABLE 1.—*Nephrosclerosis with Uremia*

| No. | Post-mortem No. | Color | Sex | Age | Anatomic Signs of Uremia | Weight of Kidneys, Gm. | Weight of Heart, Gm. | Syphilitic Aortitis | Contributory Cause of Death | Clinical Impression | Duration | Blood Chemistry | Blood Pressure | Kahn Test | Histologic Observations |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 340 | C | M | 32 | + | 225 | 550 | — | ..... | Uremia | 2 wks. | Creatinine 10; urea nitrogen 100 | 228/110 | -- | Necrosis |
| 2 | 578 | C | M | 38 | + | 294 | 680 | | ..... | Uremia | 2 wks. | Urea nitrogen 137; creatinine 8.6 | 198/140 | — | Necrosis |
| 3 | 804 | C | F | 38 | + | 260 | 400 | — | ..... | Uremia | ..... | Urea nitrogen 162; creatinine 9.2 | 232/118 | — | Necrosis |
| 4 | 358 | C | F | 49 | + | 260 | 480 | | ..... | Malignant hypertension | 1 wk. | Urea nitrogen 87; indican 4+ | 260/162 | — | Necrosis |
| 5 | 371 | C | M | 24 | + | 160 | 900 | | ..... | Bacterial endocarditis | 3 wks. | Indican 4+ | 246/176 | — | Necrosis |
| 6 | 398 | C | M | 38 | + | 280 | 465 | | ..... | Cardiorenal disease | 1 wk. | Urea nitrogen 173 | 240/130 | — | Necrosis |
| 7 | 579 | C | M | 60 | + | 340 | 435 | — | ..... | Uremia | 5 wks. | Urea nitrogen 103 | 270/210 | — | Necrosis |
| 8 | 594 | C | M | 30 | + | 310 | 630 | — | ..... | Uremia | 3 mos. | Indican 3+ | 230/180 | — | Necrosis |
| 9 | 942 | W | M | 41 | + | 160 | 475 | — | Cerebral hemorrhage | Cardiorenal disease | ..... | Indican 3+ | 220/170 | — | Necrosis |
| 10 | 82 | C | F | 65 | — | 240 | 405 | — | ..... | Bronchopneumonia | 2 mos. | Urea nitrogen 90; indican 4+ | 128/ 60 | — | Necrosis |
| 11 | 129 | C | F | 38 | — | 390 | 418 | — | ..... | Uremia | 2 mos. | Urea nitrogen 151; creatinine 8 | 198/128 | -- | Necrosis |
| 12 | 396 | W | F | 65 | + | 170 | 325 | — | ..... | Chronic nephritis | 3 wks. | Indican 3+ | 278/160 | — | Necrosis |
| 13 | 539 | W | F | 49 | + | 320 | 500 | + | ..... | Uremia | 2 mos. | Urea nitrogen 117 | 225/110 | — | Necrosis |
| 14 | 742 | C | M | 64 | + | 220 | 545 | + | Hemorrhage from acute peptic ulcer | Uremia | 2 mos. | Urea nitrogen 96; creatinine 7 | 220/150 | — | Necrosis |
| 15 | 899 | W | M | 47 | + | 313 | 500 | + | Bronchopneumonia | Uremia | 7 wks. | Urea nitrogen 75; creatinine 6.6 | 260/170 | — | Necrosis |
| 16 | 360 | C | F | 60 | + | 130 | 420 | — | ..... | Uremia | 2 wks. | Indican 4+ | 198/106 | -- | Necrosis, arteriolar only |
| 17 | 623 | W | M | 55 | + | 260 | 635 | — | Cerebral hemorrhage | Undetermined | died 5 min. after admission | | | | Necrosis, arteriolar only |
| 18 | 575 | C | F | 38 | + | 120 | 505 | — | ..... | Uremia | 2 mos. | Indican 4+ | 1230/140 | -- | Necrosis, arteriolar only |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 19 | 480 | W | F | 46 | + | 280 | 460 | + | ..... | Uremia | 1 wk. | Urea nitrogen 114 | 198/142 | — | Necrosis, arteriolar only |
| 20 | 15 | W | F | 31 | + | 380 | 710 | — | ..... | Uremia | 7 wks. | Urea nitrogen 178 | 240/120 | — | Necrosis with periarteriolitis |
| 21 | 917 | C | F | 44 | + | 190 | 510 | + | ..... | Uremia | 3 wks. | Urea nitrogen 135; creatinine 11 | 200/180 | — | Necrosis with periarteriolitis |
| 22 | 401 | C | M | 42 | + | 200 | 775 | — | Miliary tuberculosis | Malignant hypertension | 2 wks. | Urea nitrogen 107 | 174/118 | — | Necrosis; miliary tubercles |
| 23 | 531 | C | F | 31 | + | 280 | 395 | — | Pyelonephritis | Uremia | 2 mos. | Urea nitrogen 45 1 wk. before death | 230/150 | — | Necrosis; pyelonephritis |
| 24 | 324 | C | M | 53 | + | 200 | 610 | — | Bronchopneumonia | Impending uremia | 2 mo. | Urea nitrogen 100; creatinine 8 | 208/176 | — | Prestasis only; no necrosis |
| 25 | 240 | C | M | 45 | + | 225 | 585 | — | Peritonitis | Undetermined | 2 wks. | Indican 4+ | ..... | — | Prestasis; necrosis slight |
| 26 | 338 | C | M | 43 | + | 200 | 450 | — | Bronchopneumonia | Hypertensive heart disease | 3 wks. | Indican 4+ | 250/140 | — | Prestasis; necrosis slight |
| 27 | 350 | C | M | 34 | + | 390 | 550 | — | ..... | Impending uremia | 2 mos. | Urea nitrogen 105 | 234/152 | — | Prestasis; necrosis slight |
| 28 | 385 | C | M | 39 | + | 240 | 560 | + | Bronchopneumonia | Hypertensive heart disease | 3 wks. | Indican 4+ | 216/148 | .. | Prestasis; necrosis slight |
| 29 | 503 | W | F | 35 | + | 160 | 615 | + | Bronchopneumonia | Hypertensive heart disease | 3 wks. | Indican 4+ | 216/148 | .. | Prestasis; necrosis slight |
| 30 | 701 | W | M | 59 | + | 110 | 360 | — | Coronary thrombosis | Uremia | 4 mos. | Indican 4+ | 228/130 | — | Prestasis; necrosis slight; marked atrophy |
| 31 | 250 | C | F | 55 | + | 143 | 465 | + | ..... | Hypertensive heart disease | 2 wks. | Indican 4+ | 288/156 | + | Prestasis; no necrosis; marked atrophy |
| 32 | 671 | W | M | 49 | + | 113 | 480 | — | Passive congestion | Cardiac decompensation | 4 mos. | Urea nitrogen 42 | 210/140 | — | No prestasis; no necrosis; passive congestion; marked atrophy |
| 33 | 551 | C | F | 64 | + | 140 | 625 | — | Passive congestion | Impending uremia | ..... | Indican 4+ | 220/110 | — | No prestasis; no necrosis; passive congestion; marked atrophy |
| 34 | 127 | C | M | 52 | + | 175 | 460 | — | Bronchopneumonia | Impending uremia | 1 mo. | Urea nitrogen 58 | 215/150 | — | No prestasis; no necrosis; passive congestion; marked atrophy |
| 35 | 769 | C | F | 38 | + | 130 | 350 | — | ..... | Uremia | ..... | Urea nitrogen 134; creatinine 10.5 | 170/110 | — | No prestasis; no necrosis; no congestion; marked atrophy |
| 36 | 98 | C | M | 50 | + | 220 | 575 | + | Hemorrhage from peptic ulcer; passive congestion | Uremia | 4 mos. | Urea nitrogen 112; creatinine 8.7 | 180/130 | — | No prestasis; no necrosis; no atrophy; passive congestion |

vousness, slight nocturia or visual disturbances, which dragged on for from six weeks to months but which afforded no great disability to the patient. Frequently the patients were admitted with the complaints that for the last two months the symptoms had become markedly worse, with severe headaches, marked visual disturbance or cardiac insufficiency. Some cases, however, had passed abruptly into the terminal state without warning. In others, the patients dropped so quickly into coma that no history could be obtained.

The terminal uremic state was rapid, progressive and relentless. In a patient with chronic nephritis, uremic symptoms might develop and the patient might recover temporarily. In the cases of nephrosclerosis with uremia no remissions were noted once the uremic symptoms had begun. In many cases the duration of the major presenting symptoms was difficult to ascertain. The average duration is estimated at five or six weeks, with a range of variation of from one week to four months. Klemperer and Otani observed an average duration of the period of renal insufficiency of thirty-two days.

During this period, the typical symptoms of true comatose uremia were manifested. Nausea and vomiting, extreme weakness, restlessness and various psychic symptoms which progressed to apathy and coma, nosebleeds, marked anemia and nocturia were regularly noted. When ophthalmoscopic examination was performed, albuminuric neuroretinitis was found. The blood pressure rose to excessive heights, and marked retention of nitrogen rapidly developed. The specific gravity of the urine sank, and all tests showed severe impairment of renal function. In several instances, the blood chemistry was normal even two or three weeks before death. The amount of urea nitrogen would then rise to 40 or 50 mg. per hundred cubic centimeters one week before death, and by the last day or two it might have risen to 130 mg. per hundred cubic centimeters and even higher. So rapidly may this retention develop, that unless a chemical examination of the blood had been made just before death, it was found advisable to check it post mortem by determining the indican content of the blood. An indicanemia of 3 + or 4 + was considered adequate chemical evidence of uremia.[20]

*Gross Anatomic Observations.*—In most cases the gross observations at autopsy were typical of simple uremia. The characteristic observations that were accepted to establish the diagnosis of uremia were uredrosis, fibrinous pericarditis, hemorrhagic and ulcerative ileocolitis and petechial hemorrhages in the skin, the epicardium and the mucosa of the bladder. The heart was very large, far exceeding the normal

20. Monias, B. L., and Shapiro, P.: The Value of the Indican Determination in the Blood in Cases of Renal Insufficiency, Arch. Int. Med. **45**:573 (April) 1930.

limits,[21] with a firm, rubbery myocardium. The uremic picture was usually so brief that it was free from incidental noteworthy complications. In a few cases, however, hemorrhage from an acute peptic ulcer, uremic cerebral hemorrhage or focal bronchopneumonia had helped to terminate the case.

The kidneys were usually of almost normal size, each weighing about 120 Gm. The capsule was but slightly adherent. On separation, it left a diffuse, fine, evenly granular surface that was composed of small, irregular, purplish-brown elevations separated by narrow, deeper reddish-purple depressions. Bright red petechiae ranging in size from that of a pinhead to that of a millet seed were sprinkled over the surface. The hemorrhages were characteristic and served grossly to differentiate the kidneys from those in glomerulonephritis in which the hemorrhages are smaller and resemble "flea-bites." The cortex was not much reduced, being about 7 mm. in width. Surfaces made by section were light reddish-purple, mottled with lighter grayish-red areas. Cortical markings were obscure. Similar large petechiae were scattered over the sectioned surfaces and over the pelvic mucosa. The cross-sections of the arcuate arteries were thickened and gaping. The renal arteries were markedly thickened.

*Microscopic Observations.*—Microscopic examination of the kidneys revealed that fully 60 per cent of the glomeruli were unchanged; about 10 or 15 per cent were completely or partly hyalinized, and about 10 per cent conformed to the ordinary type of hypertensive glomerulus, with decrease in size, apparent increase in the pericapsular connective tissue and simplification of tufts. From 15 to 20 per cent of the glomeruli, however, were enlarged to the size of a high power field and were fully rounded. Bowman's capsular epithelium was swollen, proliferated and sometimes thrown into a few layers. Bowman's spaces were usually narrow, but they often contained a little homogeneous, oxyphilic material with erythrocytes and a few leukocytes, and sometimes were filled with large or small hemorrhagic extravasations. The glomerular tufts were enlarged just as in a nephritis, but in marked contrast to nephritis, the individual capillary loops participated irregularly in the following changes. Sometimes only a few loops were involved and sometimes all of them. When the involvement was only partial, it was most frequently seen and was most severe near the hilus of the glomerulus.

The changes consisted of a swelling and desquamation of the endothelial cells, a swelling of the basement membrane and a swelling

21. Gewert, M.: Ueber die Schwankungen des Herzgewichts in der verschiedenen Lebensaltern unter normalen und pathologischen Verhältnissen, Jena, Gustav Fischer, 1929.

and proliferation of the epithelial cells. Fine fat droplets were deposited abundantly in all elements of the thickened capillary walls. An occasional hyaline droplet was also noted. When the changes involved an entire glomerulus, it closely resembled the mild intracapillary glomerulo-

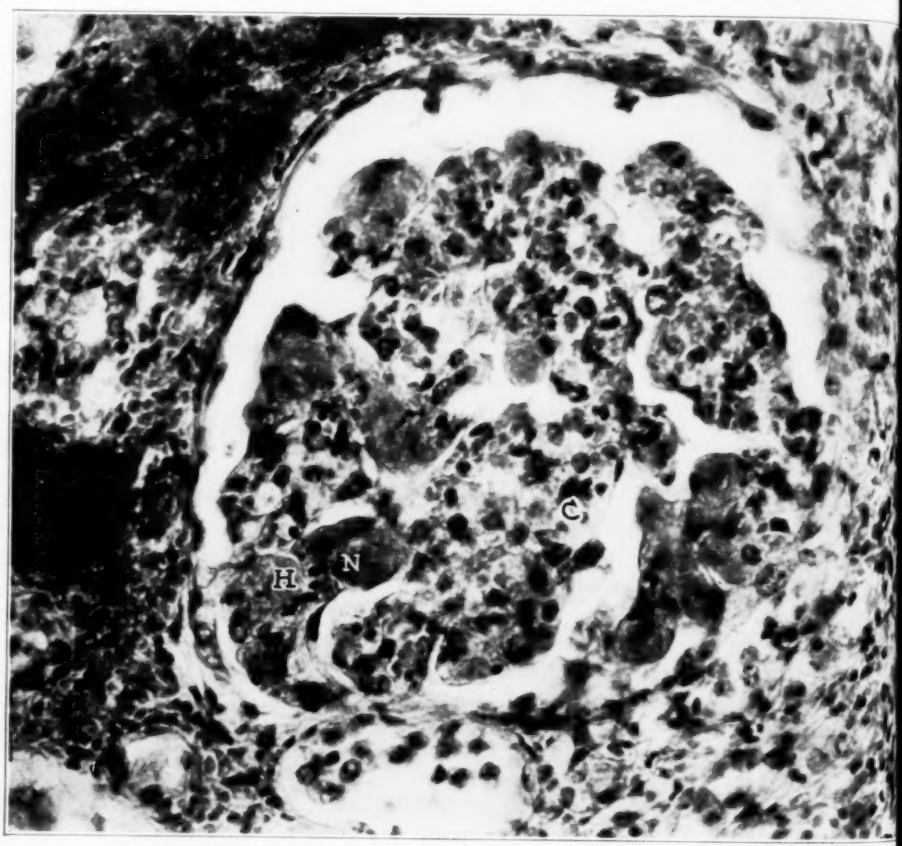


Fig. 1.—Prestatic glomerulus, with beginning necrosis. There are marked focal, capillary dilatation (*C*); slight proliferative and degenerative changes, and hyalinization of single capillary loops (*H*), and early necrosis (*N*). Note the hemorrhagic extravasation in the interstitial tissue. Leitz apochromatic 4 mm., periplanar 4, camera length 45 cm.

nephritis seen in older patients, as Klemperer and Otani pointed out. Usually, however, the changes involved only a few loops of one glomerulus and left the others unchanged. This focal character differ-

entiated it readily from nephritis in which every loop of every glomerulus is involved (Löhlein [22]).

The same irregularity was noted in the blood content of the individual capillary loops. Some of the loops had apparently collapsed and were fused together. Some of them were widely dilated with erythrocytes and with a small but varying number of leukocytes and desquamated endothelial cells. In some glomeruli, all the capillaries were widely dilated, as if the whole glomerular capillary tuft had completely relaxed; in others, only a few capillaries were dilated. When the dilatation was focal, it was most frequently seen and most severe at the hilus of the glomerulus; this condition was associated with the most marked cellular changes previously described. The most common site of the worst dilatations as well as of the most severe cellular changes was the intraglomerular part of the afferent arteriole (fig. 1).

In addition to these changes, there were certain other striking changes which affected but few of the enlarged glomeruli. In these glomeruli, single capillary loops, usually those most widely dilated and those near the hilus, showed a marked thickening and diffuse hyalinization of their walls, which in about 3 per cent of the glomeruli had advanced to an actual fibrinoid necrosis. In the hematoxylin and eosin sections, the necrotic capillary walls stained a smudgy purple, with fine deep blue granules of karyorrhectic nuclei, in contrast with the homogeneous, light pink cytoplasm and swollen, vesicular nuclei of simple hyalinization. Herxheimer [23] called attention to these differences, and demonstrated by Weigert's stain that this type of necrosis was actually associated with the appearance of a fibrinoid substance. Fat was demonstrated in abundant, irregular droplets in the necrotic walls.

Occasionally, the entire glomerulus was involved in the necrosis. Usually, however, there were only one or two necrotic loops near the hilus with numerous widely dilated, nonnecrotic loops at the periphery that showed only the proliferative, exudative and slight degenerative changes previously mentioned. The necrotic loops themselves sometimes appeared occluded, but they were usually the ones most severely dilated. When the necrosis involved many loops, there was sometimes an abundant infiltration of leukocytes; this was never seen when the necrosis was slight. In a few cases in which entire glomeruli were necrotic, fine granules of calcium were deposited, and the leukocytic reaction was marked. All of these changes were seen not only in the enlarged glomeruli, but also, occasionally, in the hypertensive glomeruli and even in the partly hyalinized ones.

22. Löhlein, M.: Ueber die entzuendlichen Veränderungen der Glomeruli menschlichen Nieren, Arb. a. d. path. Inst. zu Leipzig, 1908.

23. Herxheimer (footnote 12, second reference).

When necrosis affected a glomerulus, the intraglomerular part of the afferent arteriole was always severely involved. The extraglomerular part of the afferent arteriole also was practically always involved. But often the arteriole alone was necrotic, and either with a dilated lumen or even with an apparently obstructed lumen, led to a glomerulus that

Fig. 2.—Necrotic arteriole winding toward its glomerulus, which shows no necrosis, but only the prenecrotic proliferative changes. Despite the apparent arteriolar occlusion, the glomerulus is still viable. Leitz apochromatic 16 mm., periplanar 4, camera length 45 cm.

showed no necrosis but only the proliferative and slight degenerative changes and the focal capillary dilatation previously mentioned (fig. 2). In four cases only arteriolonecrosis was found in the kidney. The glomeruli presented all the other changes described, but no necrosis.

The arteriolar walls were thickened; they stained a smudgy purple, with fine, deep blue granules of nuclear disintegration, and they showed an extreme fatty degeneration. There was an indistinct limitation of the wall of the vessel and diffuse and localized aneurysmal dilatations. The

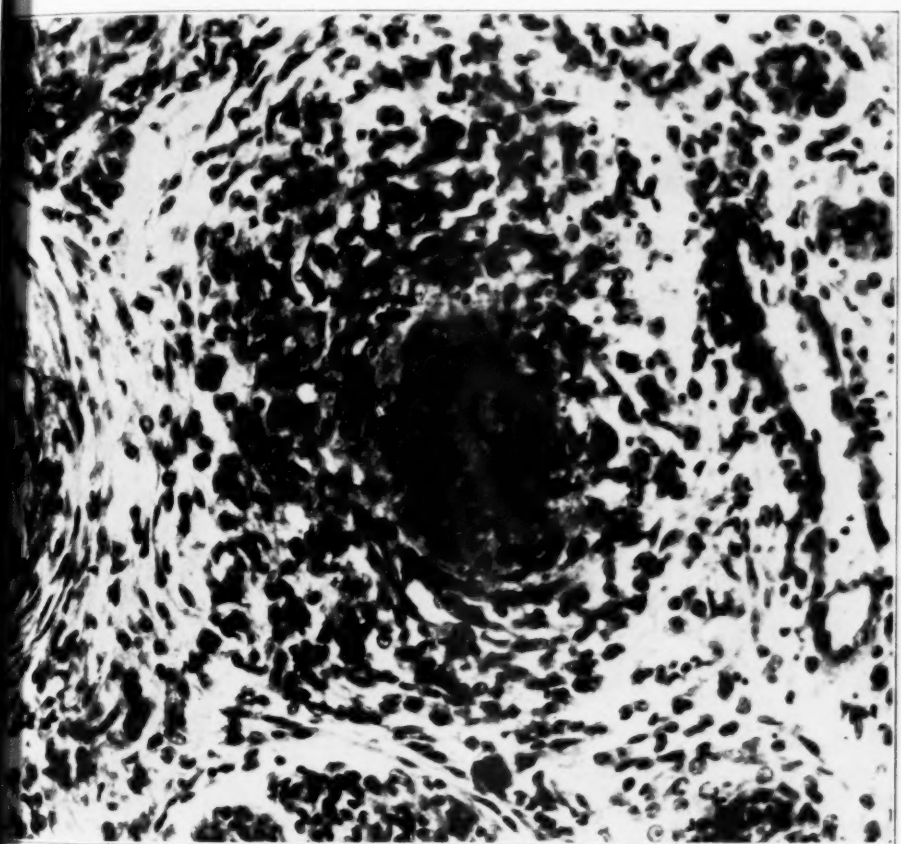

Fig. 3.—Necrotic arteriole. The arteriolar wall is impregnated by erythrocytes and leukocytes. It is surrounded by a periarteriolar nodule composed of proliferated adventitial cells and polymorphonuclear leukocytes. Leitz apochromatic 8 mm., periplanar 4, camera length 45 cm.

necrotic arteriolar walls were often impregnated by erythrocytes, and sometimes they were split by larger hemorrhagic extravasations, which extended widely into the adjacent interstitial tissue. This was the basis for the large petechial hemorrhages noted grossly. In places the arteri-

olar lumen was apparently obstructed; in other places it was only partly occluded by swollen endothelial cells, desquamated cells, erythrocytes, leukocytes and structureless débris.

Occasionally, this fibrinoid necrosis extended proximally all the way to the intima of the small interlobular arteries. In a few cases such extensive necrosis was associated with the formation of periarteriolar nodules composed of swollen and proliferated adventitial cells with a few polymorphonuclear leukocytes (fig. 3). In some cases, extensive necrosis was found without periarteriolar reaction, but the latter was found only intimately associated with severe necrosis. It was rarely present, but, when it appeared, it was directly proportional to the extensiveness of the necrosis. All transitions could be seen, from cases with moderately extensive necrosis and slight periarteriolar infiltration, to those with more extensive necrosis and the well defined picture of a periarteriolitis nodosa.

Necrosis usually involved only a small proportion of the arterioles. The remainder showed only an intimal thickening with hyaline and fatty degeneration. The large arteries, the arcuate arteries and the interlobular arteries showed a progressively more marked intimal thickening. In some branches, the thickened intima was dense, fibrotic and arranged in definite layers with elastica proliferation, as in the benign form of nephrosclerosis. This "hyperplastic intimal thickening" of Hueck[24] involved the arteries and arterioles that lead to the hypertensive and hyalinized glomeruli. In most of the vessels, however, the intimal thickening even exceeded that seen in benign nephrosclerosis; it was even more irregular and different in appearance. The intima was thick but loose, and was composed of a pale, light blue ground substance in which many star-shaped cells were loosely suspended, and in which but few collagenous and elastic fibrils were loosely scattered. The picture corresponded to the "regenerative intimal thickening" of Jores, which Hueck clearly outlined as being only a more rapidly developing form of hyperplastic intimal thickening. These vessels were associated with the enlarged necrotic or prenecrotic glomeruli described. Fine fat and hyaline droplets were deposited in the deeper layers of the thickened intima. The media was usually atrophic, but occasionally it showed an apparent slight hypertrophy.

The convoluted tubuli showed a striking degeneration of the hyaline droplets. This degeneration was practically never seen in the benign form. Many of the tubuli were filled with extravasated erythrocytes. The interstitial tissue was slightly increased focally; within it, the

24. Hueck, W.: Ueber das Mesenchym, Beitr. z. path. Anat. u. z. allg. Path. **66**:330, 1920; Anatomisches zur Frage nach Wesen und Ursache der Arteriosklerose, München. med. Wchnschr. **67**:535, 1920.

pericapsular branch of the afferent arterioles was sometimes seen to be dilated, but the efferent arterioles and the intertubular capillaries were not dilated as in cases of passive congestion.

In other organs, arteriosclerosis and arteriolosclerosis were less constantly seen. In the spleen they were common, but in this organ

Fig. 4.—Prenecrotic glomerulus in the periphery of a miliary tubercle. Note the Langhan's giant cells at the left hand edge. These were in the periphery of the tubercle. Note the hemorrhagic extravasation in Bowman's space of the glomerulus. Leitz apochromatic 8 mm., periplanar 4, camera length 45 cm.

they are physiologic in old age. These conditions were found often in the pancreas and liver and occasionally in the suprarenal gland. Necrosis was never seen outside the kidneys, except in one case, in which the spleen showed multiple areas of necrosis. The "speckled spleen"

reported by Feitis [25] had been reported only in cases of nephrosclerosis with uremia. Necrosis of the pancreas has also occasionally been reported by others.[5]

In two cases, the malignant renal changes were accompanied by other complicating renal conditions. In one case (case 22) in which there was generalized disseminated miliary tuberculosis, there were numerous miliary tubercles in the previously sclerotic kidneys. In the epitheloid zone of these tubercles and even beyond them, necrotic and prenecrotic glomeruli and necrotic arterioles were found (fig. 4). In case 23, pyelonephritis was similarly associated.

In the remaining eight cases (cases 24 to 31), there was a discrepancy in the histologic observations. The clinical picture conformed exactly with that of classic malignant nephrosclerosis. The general observations at autopsy were the same, except that there was usually some severe complication that had hastened the fatal termination. The kidneys were grossly identical, except that the petechial hemorrhages were scanty or absent. Microscopic examination revealed most of the changes already described with an even more widespread and more marked focal and glomerular capillary dilatation, with enlarged glomeruli, proliferative and degenerative changes and intimal thickenings. In some of the enlarged glomeruli, with markedly dilated capillary loops, some of the loops near the hilus showed a marked, hyaline thickening. Actual necrosis of glomeruli or arterioles could nowhere be found. In seven of these cases, the only suggestion of early necrosis was a slight smudgy purple transformation of the hyalinized capillary loops that have been described. In case 30, a marked preceding sclerotic parenchymal atrophy was also present; this atrophy had probably contributed to the renal failure.

Among the 1,000 cases in which autopsy was performed there were 42 of glomerulonephritis. Twenty-four of the patients had died in uremia, and 18 through some factor other than uremia. In the uremic group there were 4 cases of chronic nephritis and 1 of subacute nephritis which showed the same type of glomerulonecrosis and arteriolonecrosis. One case of chronic and one of subacute nephritis showed only arteriolonecrosis (table 2). In one case of rapidly progressive subacute nephritis in a child 12 years of age, there was an extensive glomerulonecrosis and arteriolonecrosis as it is seen in the most severe cases of malignant nephrosclerosis, accompanied by periarteriolitis nodosa. One case of chronic nephritis showed a focal capillary dilatation with but slight necrosis. Four cases showed the glomerular capillary dilatation with no

25. Feitis, H.: Ueber multiple Nekrosen in der Milz, Beitr. z. path. Anat. u. z. allg. Path. **68**:297, 1921.

TABLE 2.—*Glomerulonephritis with Prestasis or Necrosis*

| No. | Post-mortem No. | Color | Sex | Age | Anatomic Signs of Uremia | Weight of Kidneys, Gm. | Weight of Heart, Gm. | Syphilitic Aortitis | Contributory Cause of Death | Clinical Impression | Duration | Blood Chemistry | Blood Pressure | Kahn Test | Histologic Observations |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 149 | C | M | 34 | + | 320 | 560 | — | ..... | Chronic nephritis | 4 mos. | ..... | 210/146 | .. | Necrosis; chronic nephritis |
| 2 | 219 | C | F | 50 | + | 200 | 500 | — | ..... | Chronic nephritis | 1 yr. | Urea nitrogen 135; creatinine 11 | 300/156 | — | Chronic nephritis; necrosis |
| 3 | 834 | C | F | 43 | + | 315 | 697 | + | ..... | Uremia | 1 yr. | Urea nitrogen 106 | 194/140 | — | Necrosis; chronic nephritis |
| 4 | 791 | W | F | 43 | + | 300 | 495 | — | ..... | Uremia | 8 mos. | Urea nitrogen 93; creatinine 6 | 224/154 | — | Necrosis; chronic nephritis |
| 5 | 185 (1930) | C | F | 29 | + | 315 | 350 | — | ..... | Chronic nephritis | 5 wks. | Urea nitrogen 60; creatinine 4.6 | 254/150 | — | Necrosis; subacute nephritis |
| 6 | 113 | W | F | 12 | + | 300 | 260 | — | ..... ..... | Acute nephritis | 6 wks. | Urea nitrogen 82; creatinine 5 | 140/ 90 | — | Necrosis; periarteriolitis; subacute nephritis |
| 7 | 185 (1929) | C | M | 35 | + | 223 | 640 | + | Bronchopneumonia | Uremia | 3 mos. | Urea nitrogen 124; creatinine 9 | 255/160 | — | Necrosis; arteriolar only; subacute nephritis |
| 8 | 704 | C | M | 38 | + | 310 | 730 | — | ..... | Uremia | 3 wks. | Urea nitrogen 142 | 240/194 | — | Necrosis; arteriolar only; subacute nephritis |
| 9 | 260 | C | M | 40 | + | 275 | 590 | — | Pyelonephrosis | Uremia | 3 mos. | Urea nitrogen 139; creatinine 13 | 210/150 | — | Prestasis; necrosis slight; chronic nephritis |
| 10 | 137 | C | F | 40 | + | 275 | 500 | — | Edema of brain and lungs | Uremia | 3 mos. | Urea nitrogen 126; creatinine 12 | 190/150 | — | Prestasis; no necrosis; chronic nephritis |
| 11 | 614 | W | M | 22 | + | 500 | 375 | — | Bronchopneumonia | Uremia | 9 days | Urea nitrogen 148; creatinine 12 | 115/ 85 | — | Prestasis; no necrosis; acute nephritis |
| 12 | 61 | C | F | 40 | + | 200 | 455 | — | ..... | Uremia | 5 mos. | Urea nitrogen 70; creatinine 7 | 250/145 | — | Prestasis; no necrosis; chronic nephritis |

suggestion of necrosis. One case had progressed to uremia through advanced parenchymal atrophy. The rest showed no marked atrophy or necrosis and only an occasional dilated capillary loop. The hyaline drop degeneration of the convoluted tubuli was as striking as in the cases of malignant nephrosclerosis.

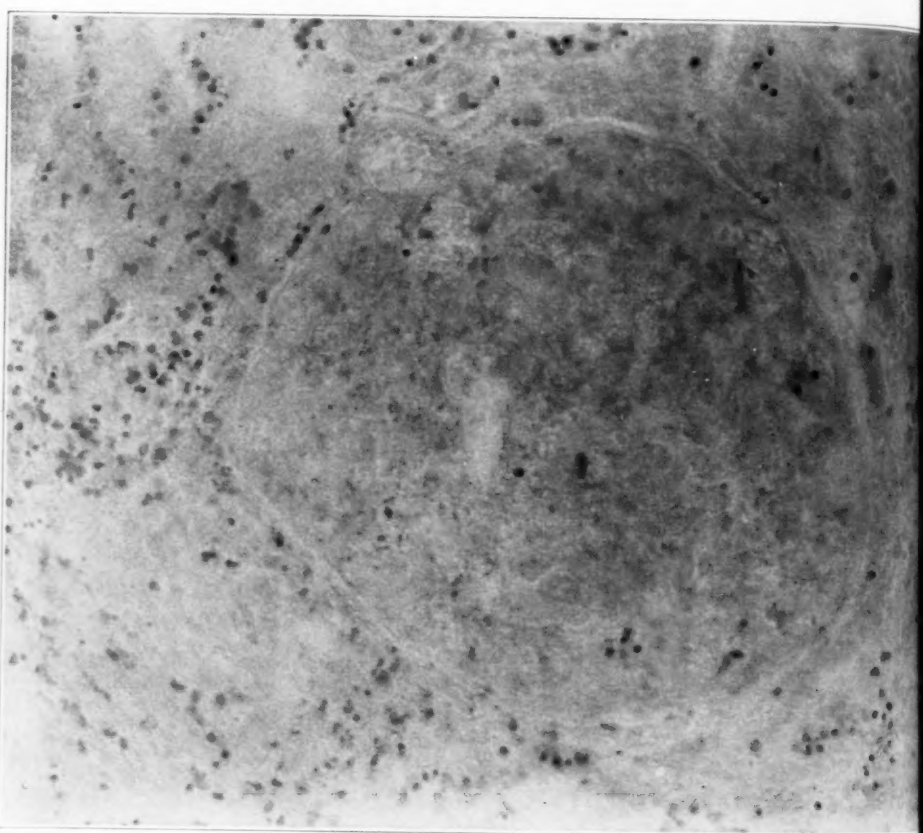

Fig. 5.—Hyaline necrosis in anemic center of an infarct. Leitz apochromatic 4 mm., periplanar 4, camera length 45 cm.

Necrosis of the glomeruli or the arterioles was never seen in any of the cases of benign nephrosclerosis. However, occasional observations of this kind have been reported by others, even by Fahr. The other changes, however, were seen more frequently. In case of benign nephrosclerosis that terminated through some factor other than uremia, an occasional enlarged glomerulus with slight proliferative and degenera-

tive changes could be found. Even more commonly, an irregular, focal, glomerular, capillary dilatation similar to but not as marked as that seen in the malignant form was noted. Here, too, it was most common and severe near the hilus of the glomerulus, and in the intraglomerular part of the afferent arteriole.[26] The eight cases of malignant nephrosclerosis

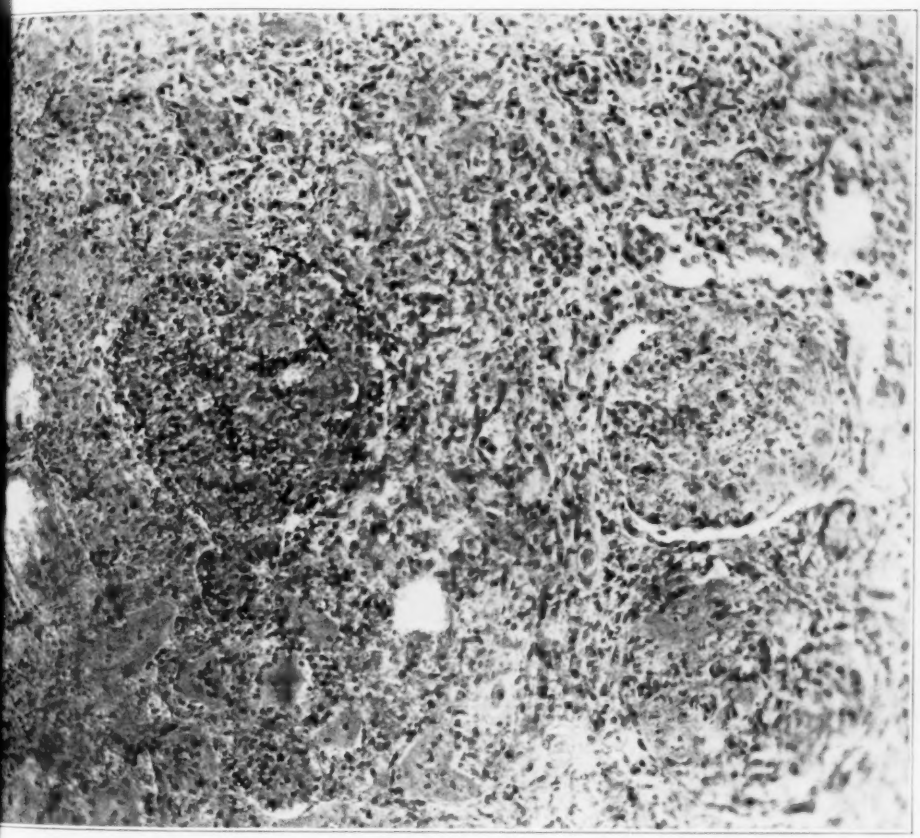

Fig. 6.—Fibrinoid necrosis in hyperemic periphery of the same infarct. Leitz apochromatic 16 mm., periplanar 4, camera lenth 45 cm.

without necrosis but with marked capillary dilatations, proliferative and prenecrotic changes presented all transitions between the cases of benign nephrosclerosis without necrosis and the cases of malignant nephro-

26. Jaffe, R. H.: The Vascular Changes of the Kidney in Hypertension, Am. J. M. Sc. **169**:88, 1925.

sclerosis with necrosis. These transitions without necrosis but with vascular dilatations strengthened the impression that benign and malignant nephrosclerosis were essentially the same, differing only in the speed of development. The feature common to all cases was the presence of irregular, focal, capillary dilatations.

The marked capillary dilatations seen in the malignant and in the transition forms and the less marked dilatations seen in the benign forms suggested, however, that something was wrong with the ischemic hypothesis. Ischemia, also, was not compatible with the proliferative changes observed. Proliferation requires an increased and not a decreased amount of nutrient fluid. Indeed, the proliferative and prenecrotic changes were found intimately associated with the most widely dilated capillaries, and not with the ischemic ones. Volhard held that the proliferative changes were reactions to ischemic degeneration, but they were often marked when there was little or no degeneration with them. Furthermore, ischemia does not produce a fibrinoid type of necrosis, but a hyaline necrosis. The swollen, oxyphilic, hyaline ghosts of glomeruli in the bloodless centers of anemic infarcts (fig. 5) are altogether different from the proliferated, degenerated and necrotic glomeruli, identical with those of malignant nephrosclerosis seen in the periphery of the infarcts (fig. 6). The glomeruli are found only in the periphery of the recent infarcts, in the zones of hyperemia and leukocytic infiltration and marked circulatory disturbances, but never in the anemic centers. Therefore, to secure a more reliable impression of the actual state of hyperemia or ischemia in the renal blood vessels of malignant nephrosclerosis, a series of injection experiments was performed.

### EXPERIMENTAL INJECTION

Renal injections have been applied many times before. All writers have concurred that in nephrosclerosis renal permeability is markedly reduced. Rigo [27] perfused normal and pathologic kidneys with horse serum at body temperature and at constant pressures. He found that, normally, from 90 to 200 cc. of serum would pass through the vessels of the kidney within five minutes. In sclerotic kidneys, the perfusibility was so markedly reduced that only from 4.5 to 8 cc. would get through within this time.

Doenecke and Rothschild [28] perfused kidneys with physiologic solution of sodium chloride at body temperature, but at varying pressures.

27. Rigo, A.: Untersuchungen über die postmortale Durchströmungskapazität des Nierenblutgefäss-Systems bei verschiedenen Erkrankungen, Frankfurt. Ztschr. f. Path. **31**:1, 1925.

28. Doenecke, F., and Rothschild, P.: Ueber das Verhalten der postmortalen Durchströmungskapazität des Blutgefäss-Systems der Niere bei Erkrankungen mit und ohne Blutdrucksteigerung, Zentralbl. f. inn. Med. **48**:866, 1927.

With normal kidneys, perfusion began at from 10 to 50 mm. of mercury and at 120 mm. amounted to 100 cc. per minute. With sclerotic kidneys perfusion did not begin until a pressure of at least from 80 to 150 mm. of mercury was used. At 150 mm., the salt solution might barely squeeze through, and at 200 mm. of mercury, the perfusion would amount to only 4 cc. or so, per minute.

Baehr and Ritter [19] reviewed the various methods of injection used. They injected barium sulphate-gelatin mixtures into kidneys and then visualized the injection by x-rays. They were able to demonstrate in the x-ray pictures of sclerotic kidneys a marked reduction in vasculature. They emphasized the circulatory embarrassment as the mechanism of renal insufficiency.

Hayman [29] has done the most recent and accurately quantitative work in this field. He measured the outflow from the renal vein during perfusion at various pressures and correlated this with roentgenograms of the vessels taken after injection and with histologic study. His conclusions were the same. For example, he found that the perfusibility of normal kidneys at 100 mm. of mercury was 1.7 cc. per gram per minute. In sclerotic kidneys, the perfusibility at 100 mm. was 0, and at 200 mm. it had reached only 1 cc. per gram per minute.

The method used here was somewhat similar to that of Hayman. Kidneys were removed at autopsy and perfused as soon as possible, usually within an hour or two. The left kidney was usually used and the right kidney was taken for the immediate gross and histologic examination necessary to establish the diagnosis. The renal artery and vein were left as long as possible. The entire kidney, embedded in its pararenal fat, together with its suprarenal gland, was tied off and removed.

The artery and the vein were cannulated. The kidney was first perfused with 2 liters of physiologic solution of sodium chloride, at 37 C., until it was washed uniformly white. An ordinary clinical baumanometer was inserted in the circuit, and the perfusion was conducted at whatever systolic blood pressure was recorded for the patient. The numerous small leaks from the small vessels of the pararenal fat tissue and especially of the renal hilus were carefully tied off.

During this preliminary washing the observations of Hayman and of Doenecke were readily repeated. Perfusion through normal kidneys occurred freely. At pressures of 100 mm. of mercury, the salt solution issued in full stream from the renal vein. With the sclerotic kidneys, even at 200 and 240 mm. of mercury, the salt solution trickled through, only drop by drop, with the greatest difficulty. If the pressure

29. Hayman, J. M.: Experiments on the Patency of the Blood Vessels of Nephritic Kidneys, J. Clin. Investigation **8**:89, 1930.

used for perfusion was allowed to fall to 180 or 160 mm., no fluid would pass through the kidneys.

When the renal vessels had been washed as clean as practicable with salt solution, an india ink solution was used for perfusion. Here the difficulty in perfusion was even more apparent than with the salt solution. The india ink flowed easily through normal kidneys, but squeezed through the sclerotic kidneys very slowly, even at high pressures. This was attributed to the somewhat greater viscosity of the ink solution. The viscosity of the ink as determined by the Hess capillary viscosimeter was 120. That of blood serum was 125. Dilution of the ink with 0.9 per cent salt solution or with 6 per cent acacia in 0.9 per cent salt solution reduced the viscosity, but gave no better end-results. Even at a dilution of 1:8, with a viscosity of 87.5, but little more ink came through. Accordingly, the conclusion was drawn that the primary vascular impairment of permeability was already so great that the differences in the viscosity of the perfusion fluid became an insignificant factor.

The perfusion with ink was maintained for about one hour. The kidneys were then fixed at once in a diluted solution of formaldehyde, U. S. P. (1:10). A small piece was also fixed in alcohol. Frozen and paraffin sections were then made of the kidney into which ink had been injected; they were stained with hematoxylin and eosin and with sudan III, and compared with the uninjected kidney of the same patient. No appreciable difference in result was obtained between the material fixed in formaldehyde and that fixed in alcohol, between the frozen sections and the paraffin sections or between the perfusions with low dilutions of india ink and those with high dilutions.

Examination of all of these sections revealed that in normal kidneys the ink was present in a large majority of the glomeruli. In the sclerotic kidneys, it was present in but a part of the glomeruli with the surprising feature that the injection of ink had particularly favored the glomeruli that were most severely involved in the malignant changes. In a given section, with 60 per cent or more of the glomeruli unchanged, few of the normal glomeruli contained ink. Of the 20 per cent or so of partly hyalinized or hypertensive glomeruli, a somewhat larger number contained ink, and these were usually the ones with the early malignant changes. The enlarged glomeruli, numbering only 15 or 20 per cent of the total, presented the greatest actual number of injected ones. The more severely damaged the glomerulus, the greater was the amount of ink that had accumulated within it (fig. 7).

Not only did the ink favor the pathologic glomeruli over their more numerous, normal neighbors, but in a single glomerulus, the ink was most abundant at the site of the most severe changes. If only a few capillary loops were involved in proliferation and focal dilatation, the ink appeared only in those loops. If only one or two loops near

the hilus were necrotic, the ink was found within these necrotic loops, and less abundantly, or not at all, in the less severely involved, more peripheral ones (fig. 8).

With the injection of ink it was found that the arterioles that were apparently occluded in the uninjected specimens possessed widely filled

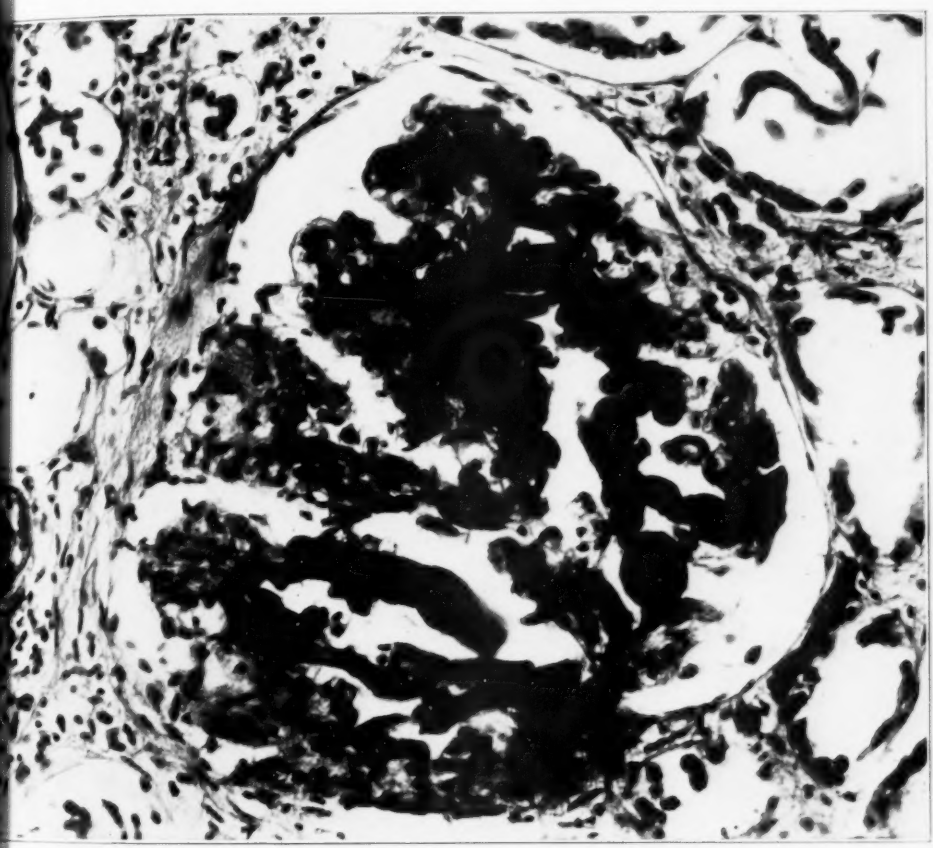

Fig. 7.—Prenecrotic glomerulus injected with india ink. Note the severe capillary dilatations, approaching an almost complete relaxation. Leitz apochromatic 4 mm., periplanar 4, camera length 45 cm.

lumina. Necrotic arterioles with dilated lumina filled by ink led freely into their corresponding necrotic or prenecrotic glomeruli. Adjacent normal or hyalinized arterioles with their normal, hypertensive or hyalinized glomeruli were more often empty of ink.

So far it was apparent that the more severe the glomerular changes, the greater was the amount of blood contained in the involved capillary loops. This was checked by the injection of ink which had accumulated most abundantly in the loops that were most severely damaged. It could therefore be concluded that hyperemia, not ischemia, was associated with

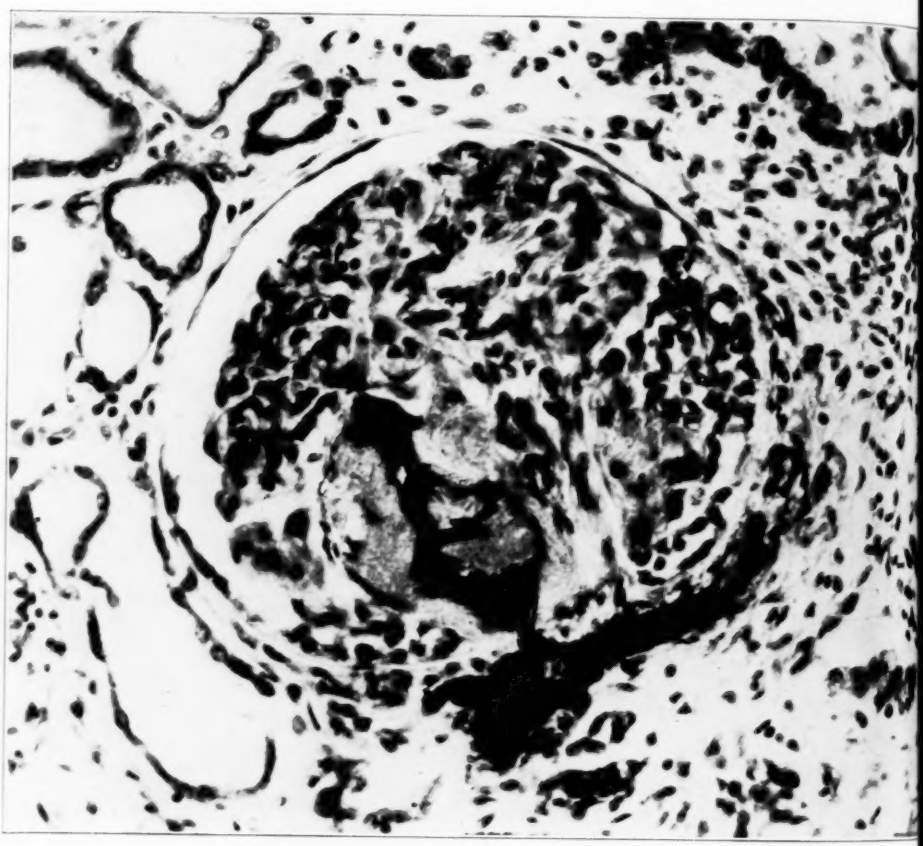

Fig. 8.—Necrotic glomerulus injected with india ink. The ink is seen just within the capillary loop that is most extensively necrotic. It is seen also in the dilated afferent arteriole and in the pericapsular branch of the afferent arteriole, but it had not reached the efferent arteriole or the intertubular capillaries. Leitz apochromatic 8 mm., periplanar 4, camera length 45 cm.

these malignant changes. Klemperer and Otani had already noted the vascular dilatations in malignant nephrosclerosis, but had explained them on the basis of back flow from adjacent normal glomeruli, through the efferent arterioles.

Fig. 9.—Specimen from serial sections in which the injection of ink could be followed from the interlobular artery directly through the necrotic, dilated, afferent arteriole into the prenecrotic glomerulus. Leitz apochromatic 8 mm., periplanar 4, camera length 45 cm.

Since with all the difficulty of injection, ink was found most abundantly in the necrotic glomeruli, it is unlikely that it could have reached them by back flow from their normal neighbors. That this hyperemia was not a result of back flow was further indicated by the fact that the ink was found more abundantly at the hilus of the involved glomeruli than at the periphery, and finally by the fact that little or no ink was found in the efferent arterioles or intervening intertubular capillaries.

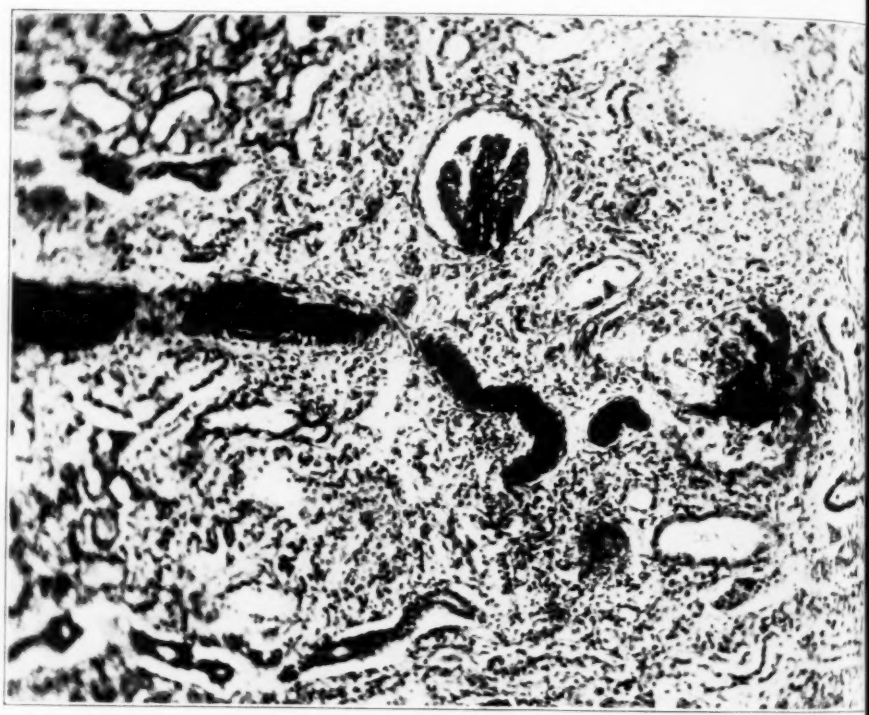

Fig. 10.—Specimen from serial sections in which the injection of ink could be followed from the interlobular artery directly through the necrotic, dilated, afferent arteriole into a diffusely necrotic glomerulus. An adjacent normal glomerulus is uninjected. Leitz apochromatic 16 mm., periplanar 4, camera length 45 cm.

To confirm this point, however, serial sections were made from the specimens into which injections had been made. In these sections, the injected ink could be followed clearly from the intertubular artery directly through the necrotic afferent arteriole into the necrotic (fig. 10) or prenecrotic (fig. 9) hyperemic glomeruli. Occasionally it was traced into the pericapsular branch of the afferent arteriole (fig. 8), but it

never originated in the efferent arterioles or intertubular capillaries. The hyperemia was therefore conclusively direct and not retrograde.

## COMMENT

It was difficult to reconcile these observations. Nephrosclerosis is undeniably associated with ischemia. Even the experiments described showed the extreme slowness and difficulty with which blood passes through these kidneys at even very high pressures. Also the impaired permeability during life is almost certainly the basis for the renal functional insufficiency. Ischemia exists and may well be accepted as the cause of the uremia. But ischemia as such is not the basis for the characteristic pathologic changes. These changes were intimately and proportionately associated, not with ischemia, but with a direct hyperemia.

The confusion arose from failure to recognize that vascular dilatation does not necessarily denote hyperemia. It is an example of the failure of morphologic investigation when unsupported by physiologic correlation. What really existed was a hyperemia in the sense that a given portion of the vascular tree at any one time contained a greater quantity of blood, but an ischemia in the sense that the blood was passing through these vessels much more slowly than before. What really occurred was a hyperemia with retardation, just as it is seen in any inflammatory lesion (Fähraeus [30]). The retardation may proceed to complete stasis. For the less severe degrees of this condition, Jaffe suggested the term "prestasis." The vessels are widely dilated, the blood is flowing through them very slowly or not at all.

Gustav Ricker [17] first propounded this conception to explain the paradox that I encountered of hyperemia associated with ischemia. He based his conclusions on direct studies on the living animal and on occasional observations on human beings during surgical operation. According to his views, the arteries, arterioles and capillaries are innervated organs, with a double nerve supply regulating constriction and dilatation. Moderate stimuli produce moderate contraction; strong stimuli produced marked contraction; excessive stimuli produce a loss of contrictor tonus, with paralysis. Dilator tonus is less sensitive and is retained after constrictor tonus is lost. Excessive stimuli, therefore, result quickly, not in contraction, but in dilatation.

The arterial tree reacts segmentally. Its peripheral portions are progressively more sensitive than the proximal portions. A stimulus that is sufficiently strong to cause marked contraction of a larger artery constitutes an excessive stimulus for the capillaries and arterioles and

30. Fähraeus, R.: The Suspension Stability of the Blood, Physiol. Rev. **9**:241, 1929.

results in their dilatation. This dissociation in reaction between arterial contraction and peripheral dilatation is not always uniform. But whenever and wherever it occurs, there is a marked decrease in the velocity of flow through the involved, dilated, peripheral bed. The narrowed arterial stream is retarded as it enters the dilated arteriole and capillary, just as the current of a river slows down when it empties into a lake. The greater the peripheral dilatation, the greater will be this retardation.

This dissociation in reaction is the normal vascular neurogenic mechanism by which the vessels of an organ regulate the total blood supply, and by which the blood supply to the various functional units is constantly being shifted and changed. These rapid vascular changes play a particularly prominent rôle in the kidney, in which rapid functional changes are constantly going on, as part of the mechanism to insure physiologic hemostasis of the organism (Cannon [31]).

Only on exaggeration of this normal, neurogenic, vascular mechanism do organic pathologic changes follow. The nutrition of the vascular walls and of the adjacent tissues depends on the speed with which blood is flowing through their lumina and partly also on the adventitial supply which is being similarly regulated. Constriction of the artery gives a more rapid flow of blood and with it a faster interchange of nutrient fluids between the lumen and the wall. With dilatation, the blood stream is retarded, and two changes follow: (1) a liquor diapedesis, an imbibition of the walls with an increased amount of nutrient fluid, and (2) a decrease in rate of interchange of nutrient fluids between the lumen and the wall. The increased amount of imbibition of fluid favors cellular proliferation and swelling. The decreased rate of the interchange of fluid favors degenerative changes. These two factors vary in the importance of their effect with the degree of dilatation and slowing.

If the peripheral dilatation is moderate, there is moderate retardation and a moderately increased amount of imbibition of fluid within the vascular walls. This is adequate for only a limited cellular proliferation within the somewhat thickened vascular walls, but a more marked elastic and collagenous fibrillar differentiation slowly takes place. The decreased rate of interchange of fluid favors the slow deposit of elastin and collagen and, finally, of a small amount of hyalin and fat. The prolonged retardation finally ends in slow atrophic changes.

If retardation is marked, there is a marked imbibition of the walls of the vessels with nutrient fluid. They rapidly become much swollen. The markedly increased amount of nutrient fluid within them determines an active proliferation of the young, star-shaped, mesenchymal

31. Cannon, W. B.: Organization for Physiological Hemeostasis, Physiol. Rev. **9**:399, 1929.

cells, while as yet only a few scattered fibrils have had time to differentiate. Fat is abundantly deposited because of the factor of decreased rate of interchange of fluid.

Severe dilation brings with it a severe retardation of flow. There is an even more marked imbibition of fluids, so that the vessels become much swollen with it. But the decrease in rate of interchange of fluid is now so great that even the increased amount of nutrient fluid rests sluggishly within the swollen walls of the vessels. It is valueless for cellular proliferation, and only a marked fatty and hyaline degeneration occurs. Finally, with extreme dilatation there is almost complete stasis of flow. The walls of the vessels swell up with fluid, but the extreme retardation of interchange of nutrient fluid establishes a complete cessation of the nutrient supply to the vascular wall. The viability of the vascular wall is imperiled, and as fibrin is deposited from the imbibed fluid a fibrinoid necrosis finally results.

As the stream slows down, not only liquor diapedesis, but erythrodiapedesis takes place; red blood cells and even leukocytes filter out of the dilated lumen through the walls of the vessels into the tissue spaces (see Fähraeus [30]). Even before necrosis takes place, this erythrodiapedesis in the glomeruli and arterioles may thus result in moderate hematuria and small petechiae in the kidney. When necrosis finally occurs, the walls of the dead vessels given way under any returning pressure of blood, dilate and break, so that the larger, petechial, hemorrhagic extravasations of malignant nephrosclerosis are formed. If the patient still lives, leukocytes accumulate about the necrotic walls of the vessels, and even calcium salts may be deposited from the blood stream in the partly necrotic tissues. With prestasis sufficiently severe to cause an extensive arteriolar necrosis, there is a similar circulatory and nutritional disturbance in the periarteriolar tissue. The adventitial cells proliferate in response to the imbibition of fluid, and with the leukocytes which accumulate about the walls of the necrotic vessels, form periarteriolar nodules. The periarteriolitis is thus only a later stage of extensive necrosis. Ricker similarly accounted for the changes of periarteritis nodosa on a similar vascular and periarterial, prestatic mechanism (Ricker [17] and Gruber [32]).

All of the pathologic changes that appear in benign and malignant nephrosclerosis may thus be accounted for on the basis of various degrees of the mechanism of retardation. In benign nephrosclerosis, the dissociation in reaction between arterial contraction and peripheral dilatation is moderate. The retardation, the nutritional impairment and the consequent changes are slight; drawn out over a long period, they

32. Gruber, G. B.: Periarteritis nodosa, Virchows Arch. f. path. Anat. **258**: 441, 1925.

slowly induce a hyperplastic intimal thickening of the arteries and arterioles and a gradual hyalinization and atrophy of the glomeruli. In malignant nephrosclerosis, the dissociation is marked and the dilatations are extreme; finally the retardation approaches almost complete stasis. The nutrient supply is markedly reduced in the dilated vessels, and severe changes rapidly result. There is at first a loose intimal swelling with cellular proliferation from the factor of increased amount of imbibition of fluid. As complete stasis is approached, the factor of decreased rate of interchange of fluid predominates, proliferation stops and severe fatty and hyaline degeneration and finally fibrinoid necrosis result.

Exactly the same mechanism is responsible for the changes seen in nephritis, in periarteritis nodosa or in inflammations anywhere in the body. Ricker pointed out that the ischemia of nephritis is a postmortem illusion, brought about by agonal vascular emptying in the hypertonic organ. When accidentlly observed during life, nephritic kidneys are hyperemic. When biopsies are taken from them, they bleed much more furiously than do normal kidneys. What actually occurs in nephritis is a retardation hyperemia. The proliferative, exudative, degenerative and even necrotic changes that are seen are based on the same mechanism as that in benign or malignant nephrosclerosis, except that it is more diffuse. In nephritis, the vascular dissociations involve uniformly every capillary loop of every glomerulus.

The resemblance of malignant nephrosclerosis to nephritis, as well as its resemblance to benign nephrosclerosis and the occasional transition between them all is therefore not surprising. All these pathologic processes are based, not on ischemia as such, but on the same mechanism of retardation hyperemia resulting from excessive dissociation between arterial contraction and peripheral dilatation. In nephritis the process is moderate. The proliferative, exudative and slight degenerative changes of moderate retardation predominate. But the process is so diffuse that though it is moderate in degree, the entire kidney is at once thrown out of function, and uremia quickly develops. The necrosis of severe prestasis is infrequently seen and then only in the violent cases with "sturmischen Verlauf" (stormy course), or in older patients with a predisposing arteriolosclerosis.

In benign nephrosclerosis, the process is moderate. It is also not ischemic, but is based on hyperemia with prolonged retardation. It is moderate but focal, so that most of the kidney is still left to carry on renal function. In malignant nephrosclerosis, the process is focal and irregular, but so severe is the vascular upset that renal function is stopped and necrotic lesions appear. So rapid is the onslaught that cases are rarely found in the transitional stages before the condition has led to death from uncomplicated uremia. Occasionally, benign nephrosclerosis may be found in which there is a single necrotic lesion or

which on the verge of an impending, malignant acceleration of the renal, vascular, prestatic process is carried off by some vascular or extravascular complication affecting some other vital organ.

There is thus no fundamental difference between the pathogenesis of benign or malignant nephrosclerosis or even of glomerulonephritis. In all, there is hyperemia in the sense that because of peripheral vascular dilatations a greater quantity of blood is present at any one time, and ischemia in the sense that the flow of blood is markedly retarded through the involved vessels. In pathogenesis, nephritis and benign and malignant sclerosis are based only on varying degrees of speed and diffuseness of the same vascular mechanism of hyperemia with retardation.

The differences in etiology are unknown. In one of the cases reported miliary tuberculosis seems to have induced the severe prestatic changes that led to malignant sclerosis. In another case, pyelonephritis may have done the same. Volhard [33] suggested a constitutional or acquired angiospastic factor, with circulating epinephrine or peptones as its ultimate cause. Ask-Upmark's five cases of juvenile malignant nephrosclerosis indicate the existence of some inherited endogenous predisposition. Whether or not there is some toxin as the ultimate cause of the excessive stimuli which produce the malignant angiospasms and extreme vascular dissociations and what that toxin may be is not as yet determined and cannot be answered in this paper. Lead has been suggested.[34] Plumbism accelerates vascular sclerosis, but does not lead especially to malignant sclerosis. Syphilis has long been accepted as an important factor of nephrosclerosis in general. Fahr considered it especially important in malignant nephrosclerosis. Herxheimer, Aschoff, Volhard, Keith and his associates [35] and Klemperer and Otani, working perhaps with different material, could not confirm this theory. The material in this paper indicates that syphilis predisposes to nephrosclerosis in general, but not to malignant nephrosclerosis in particular. Fahr considered rheumatic arthritis important. A diet high in proteins,[36] gout, diabetes, alcohol and tobacco have all been suggested, but not proved, as factors.

33. Volhard, F.: Die doppelseitigen hematogenen Nieren-Erkrankungen, Berlin, Julius Springer, 1918.

34. Battaglia, F.: Il rene saturnino, Policlinico (sez. med.) **34**:153, 1927. Pejic, S.: Nature of Primary Renal Lesion Produced by Lead, Ann. Int. Med. **1**:577, 1928.

35. Keith, N. M.; Wagner, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141 (Feb.) 1928.

36. Nuzum, F. R.: Changes in Kidney in Animals with Increased Blood Pressures while on High Protein Diets, Arch. Int. Med. **40**:364 (Sept.) 1927.

Whatever its etiology, the pathogenesis of malignant nephrosclerosis begins with the advent of a generalized arterial hypertonicity, which brings with it hypertension. The hypertension, at first transient, later becomes more or less permanent and may continue for years without further changes in the arteries. The heart hypertrophies. Studies of the nail beds show inconstant changes in the capillaries (Kylin,[37] Volhard[38] and Klingmüller[39]). Whether or not sclerosis develops in the arteries and which vascular bed is selected depends, not on generalized arterial hypertonus itself, but on local, peripheral, vascular dissociations.

If these dissociations affect the kidneys in particular (the kidneys are particularly susceptible because of their double capillary system and excessive functional strains) and if they affect them moderately, a benign nephrosclerosis slowly develops. With this atherosclerosis renum lenta, renal function is still fairly well maintained, though there may be transient periods of relative insufficiency as the process slowly and erratically progresses (Klein,[40] Major[41] and Mark[42]). In this prodromal, hypertonic stage, the patients are sturdy, plethoric and healthy, despite their permanent high blood pressure. They may continue to engage in heavy manual labor, and the only warning of the malignant character of the hypertension may be an albuminuric retinitis, which may appear even a year before the fatal issue. The robust ruddiness of these patients suggested to Volhard the clinical term of "red" hypertension. Most of these cases are terminated by cardiac failure, coronary accident, cerebral vascular accident or some vascular accident.

With this predisposing basis, after a long or short prodromal period, the remaining cases slowly or rapidly progress to malignant nephrosclerosis. The same but more violent, etiologic, toxic-irritative factor or some other etiologic factor rapidly releases an exaggeration of the same vascular dissociations with more marked retardation hyperemia. Focal, proliferative, exudative, degenerative and finally necrotic lesions result in the development of atherosclerosis renum accelerata. Studies of the nail beds show intermittent vascular spasms and even organic changes. This is the terminal hyperkinetic stage. The marked vascular upset

37. Kylin, E.: Studien über das Verhalten des Kapillärdrucks im besonderen bei arteriellen Blutdrucksteigerungen, Zentralbl. f. inn. med. **41**:505, 1920.

38. Volhard, F.: Bemerkungen zu der vorstehenden Mitteilung von Kylin, Zentralbl. f. inn. Med. **41**:512, 1920.

39. Klingmüller, M., and Nevermann, H.: Capillärstudien, Ztschr. f. d. ges. exper. Med. **66**:734, 1929.

40. Klein, O.: Ueber die Rolle der transitorischen Niereninsuffuzienz im Krankheitsbild der arteriosklerotischen Hypertonie, Med. Klin. **22**:1212, 1926.

41. Major, R. H.: Kidneys in Arterial Hypertension, Am. J. M. Sc. **176**:637, 1928.

42. Mark, A. E.: Kidneys and Arterial Hypertension, M. J. & Rec. **131**:206, 1930.

throws the kidneys out of function. Chemical examination of the blood discloses marked nitrogenous retention. The patients turn weak, toxic and markedly anemic. The "red" hypertension of Volhard thus changes to a "pale" hypertension, as absolute renal insufficiency closes the nephrosclerotic picture with uremia.

## CONCLUSIONS

There is no fundamental difference in the pathogenesis of benign and malignant nephrosclerosis, whatever their respective etiologies may be. Both depend, however, not on glomerular ischemia or on arteriolar occlusion, but on a hyperemia associated with a retardation of flow. This conclusion was suggested by a histologic study, checked by a series of experimental injections. The retardation is based on a neurogenic dissociation in reaction between arterial constriction and peripheral dilatation. The changes that follow are analyzed on the basis of Ricker's views on renal hemodynamics. Moderate retardation leads slowly to the organic changes of benign nephrosclerosis. Severe retardation rapidly induces the pathologic changes of malignant nephrosclerosis and terminates in uremia. Malignant nephrosclerosis is therefore accepted simply as an "atherosclerosis renum accelerata gravis."

# BODY TYPES IN WOMEN OF INFERTILE CONSTITUTION

## THE VALUE OF SURFACE AREA PROPORTIONS AS AN ANTHROPOMETRIC METHOD OF DIFFERENTIATION *

SAMUEL GORDON BERKOW, M.D.
PERTH AMBOY, N. J.

Reproduction, metabolism and growth are not wholly independent activities of the body. Throughout life they exert a varying influence on one another.[1] The relation is not always apparent; yet conception, the supreme moment of sexual activity, is the most potent of the stimuli of growth. It initiates an orderly extension and division of the mass which are not ended even at maturity, for in the phenomenon of repair they continue, with diminishing force,[2] throughout life.

The relation between the generative and vegetative functions is not direct. On the strongest evidence, the mediacy of endocrine glands is assumed. At puberty, entrance of a sex hormone secretion into the body economy is accompanied by rapid growth, both general and sex specific, and by changes in the configuration of the body.[3] However, according to Nicola Pende,[4] pure, dominant, constitutional insufficiency of the sex glands is seldom found. More frequently encountered are "constitutional anomalies of other endocrine glands which have a very great influence on sexual development, such as the hypophysis, thyroid, thymus, the adrenals or the pineal body." In Ruffini's apt phase, form is the plastic image of function, for these glands influence the sex glands or the sex organs on the one hand, and growth and configuration of the body on the other.

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1. Frank, R. T.: The Female Sex Hormone, Springfield, Ill., Charles C. Thomas, 1929, p. 7. Schroeder, R.: Deutsche med. Wchnschr. **55**: (Jan. 4) 1929; abstr., Surg. Gynec. Obst. **50**:26 (Jan.) 1930.

2. Demonstrated mathematically by Carrel, Du Noüy and Hartman: Cicatrization of Wounds, J. Exper. Med. **24**:429 and 451 (Nov.) 1916.

3. The surface area proportions at puberty have been investigated by me in the public schools of Perth Amboy, N. J., the Kiddie Keep Well Camp of Middlesex County (N. J.), and at private camps, with the cooperation of J. Peretzman, M.D., Fanny Sender, M.D., Murray Jacobson, B. A., and Edward Margaretten, B.Sc.

4. Pende, Nicola: Constitutional Inadequacies (translated by S. Naccarati), Philadelphia, Lea & Febiger, 1928, p. 200.

The first influence is internal and is expressed in altered functions; in the instance under consideration, infertility. The second influence is external and visible. Moreover, the various glands that are known to influence the body type do so in a definite and characteristic manner.

The association of infertility with certain body types was noted by Hippocrates:[5]

> Women may be judged of whether they are in a fit state for conception or not by attending the following circumstances: in the first place to their shapes. Women of smaller stature more readily conceive than taller persons: the thin than the fat.

Karl Pearson,[6] brilliant co-founder with Frances Galton of the science of biometrics, concluded from statistical studies that tall women procreate faster than small women. This contradiction is more apparent than real, for recently Frank[7] distinguished four types among infertile women, to which the vast majority conform: (1) the typical, normal feminine, (2) the infantile, (3) the neuter and (4) the pseudomasculine. Dr. Frank's observations concur with modern conception of the influence of the endocrine glands.

In the present investigation I sought to apply a clinically available anthropometric method to Dr. Frank's material. For reasons to be stated presently, the requirements seemed to be met by Du Bois'[8] linear formula for the determination of the surface area, and especially by the proportions derived therefrom.

The advantages of mathematical expression are too obvious for discussion. It must be noted, however, that the method pursued is not exhaustive. Not all of Dr. Frank's observations are thus quantitatively expressed. Hirsuties, height and thickness of the symphysis pubis and the height of the palate arch, for instance, are not measured. Less tangible similarities and differences, often difficult even to state clearly, must always remain to the perception and astuteness of the diagnostician, yet the method has the advantage of its limitations, for more complicated mathematical data would be a distinct disadvantage.

The surface area proportion method provides a fairly simple clinical means of expressing exactly and adequately certain fundamentals of bodily build and symmetry.

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5. Adams, F.: The Genuine Works of Hippocrates, New York, William Wood & Company, 1921, vol. 1, p. 220.

6. Pearson, quoted by Garrison, F. H.: History of Medicine, ed. 2, revised, Philadelphia, W. B. Saunders Company, 1917, p. 708.

7. Frank, R. T.: Endocrine Causes of Sterility in Women, Surg. Gynec. Obst. **45**:189 (Aug.) 1927.

8. Du Bois, Delafield, and Du Bois, E. F.: Clinical Calorimetry: The Measurements of the Surface Area of a Man, Arch. Int. Med. **15**:868 (May) 1915.

The purpose of this investigation was therefore twofold: (1) to test the method under clinical conditions and, at the same time, (2) to differentiate and group by this means the body types of women of infertile constitution.

Fifty cases of primary sterility were available for this study. Each case had been thoroughly worked up by the staff of the sterility clinic. The male partner had been exonerated by the Hühner test, many actively motile spermatozoa being recovered from both the vagina and the cervix. Pelvic examination gave negative results except for hypoplasia in 28 per cent of the cases. One or more Rubin tests demonstrated the patency of the tubes; tubal peristalsis, recorded by the kymograph, was not equally active in all cases. Special investigations, for the most part ordered by the staff of the endocrine clinic, included blood counts, basal metabolism, roentgenograms of the sella turcica, visual fields and examinations of the color vision, the Janney test for carbohydrate metabolism and determination of the female sex hormone. Investigations were possible in a large proportion of the cases.

To the group complaining of sterility I have added nineteen single women referred to the endocrine clinic for severe grades of amenorrhea. Rubin [9] recently discussed the association of long delayed and scanty menses with sterility. In a large series, he found that

> Menses are habitually delayed or scanty in 3.5 to 8 per cent of gynecologic patients and in about 10 per cent of patients whose marriage is sterile. These patients are more apt to be sterile than normally menstruating women, the primary sterility varying between 30 and 70 per cent; and the total sterility, including secondary sterility, amounting in some groups to as high as 93 per cent.

In the present series of fifty selected cases of nonmechanical primary sterility, eighteen presented serious menstrual deficiency (36 per cent). Amenorrhea, oligomenorrhea and hypomenorrhea, of the serious grades, are often associated with lowered fertility.

Of the nineteen single women in this series, two had primary amenorrhea, one had had amenorrhea for fifteen years, three had had amenorrhea for one year or more (of these, one girl, 19 years old, had menstruated twice), three had had amenorrhea for from six months to one year and the remainder complained of oligomenorrhea and habitual amenorrhea of from six weeks to six months' duration. In this group there were several well marked types, which was an additional reason for its inclusion.

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9. Rubin, I. C.: Ovarian Hypofunction, Habitually Delayed and Scanty Menstruation, in Relation to Sterility and Lowered Fertility, Am. J. Obst. & Gynec. **18**:603 (Nov.) 1929.

METHOD

The surface areas of the seven chief natural divisions of the body are determined by the linear formula of Du Bois.[8] These divisions are: the head (including the neck), the trunk, the arms, the hands, the thighs (including the buttocks), the legs and the feet. From two to four measurements, lengths and circumferences, mostly from bony points, are made on each part, there being nineteen measurements in all. From these, the surface areas are computed, a constant being used for each part, which has been determined by experiment. From the actual surface areas and the total surface of the body (the sum of the seven

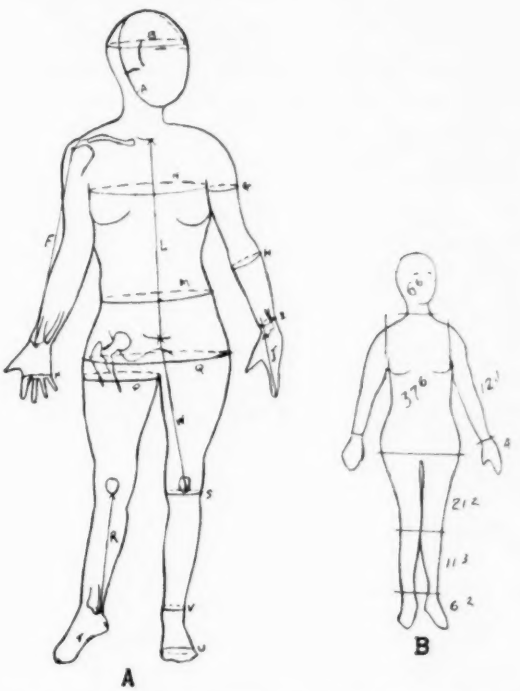


Fig. 1.—Method of obtaining measurements of surface area (after Eugene F. Du Bois and Delafield DuBois). *A* shows the method of obtaining measurements; *B*, the surface area proportions in normal persons (not the "normals" of the present series). (From the author's illustration in Frank, R. T.: The Female Sex Hormone, Springfield, Ill., Charles C. Thomas, 1929.)

parts), ratios of the parts, or the surface area proportions, are easily calculated (fig. 1).

The direct measurements of the length and circumference of each part, from which the actual surface is computed, express a relation within the parts. The actual surface areas of the parts from which the proportions are determined furnish information on each part considered by itself. Finally, the surface area

proportions show the relation between the parts. Thus, in arriving at the surface area proportions one obtains three series of figures, each of which has been applied to the grouping of the cases.

Before stating the observations in the present series, it may be well to review briefly the information at hand before this study began.

In the first place, references to the proportions alone were found. I do not know of any previous study in which relative and actual areas and direct measurements were used.

The proportions were known to be sufficiently constant in healthy persons to permit the establishment of normal average proportions.[10]

It was known that age primarily and then nutrition and sex influence the surface area proportions:

1. From birth [11] to about 18 years, the proportion of the head varies inversely to the age (from 18 to 6.5 per cent), and that of the lower extremities, progressively with the age, whereas the proportion of the trunk shows a slight gradual decline (from 38 to 36 per cent), and that of the upper extremities, a slight increase.

2. The proportion of the head, relative to the total surface of the body, varies inversely as the state of nutrition: the stouter the person, the smaller is the proportion of the head. This seems to be true also of the proportion of the lower extremities. As is to be expected, the proportion of the trunk varies directly as the state of nutrition. There is no evidence of a noteworthy influence of nutrition on the ratio between the surface area of the upper extremities and of the whole body. The surface area proportion of the hands relative to the total for the upper extremities varies inversely as the state of nutrition.

10. C. R. Bardeen (The Height-Weight Index of Build in Relation to Linear and Volumetric Proportions and Surface Area of the Body During Post-Natal Development (Contributions to Embryology, no. 46), Bull. Carnegie Institute **9**: 501, 1920) quoted the great Belgian anthropologist, Quetelet, who obtained, from actual measurements of the entire surface, the surface area proportions in a considerable group of people: "At a given stature and a given stage of physiological development the mean proportions of the human body are strikingly similar in diverse races. The similarities are so great that extensive careful statistical studies are necessary to prove conclusively that certain bodily proportions are characteristic of one race as opposed to another race. There is far more variation in rapidity of growth and in mean average adult stature in various races and social groups than there is in proportions of the body relative to stature at a given stage of physiological development." That these observations did not stimulate further investigations of the surface area proportions must be attributed to the extreme difficulty of obtaining surface area directly from actual measurements, by triangulation or from molds.

11. Berkow, S. G.: A Method of Estimating the Extensiveness of Lesions (Burns and Scalds) Based on Surface Area Proportions, Arch. Surg. **8**:138 (Jan.) 1924.

3. The head has a larger surface area proportion in females than in males. The hands constitute a larger part of the total body surface in males (5.1 per cent) than in females (4.4 per cent), but they constitute a smaller part of the upper extremities than do the hands of the females. The thighs constitute a larger percentage of the lower extremities and of the total surface in the female than in the male. However, the legs and feet of females are smaller than those of males, both actually and in relation to the total surface. The arms of males are larger than those of females, actually and relatively.

It was suspected [12] that deviations from the normal proportions (age, nutrition and sex being considered) are caused by disturbances of the endocrine glands or by disease of the neurotrophic or osteogenic system.[13]

I arrived at these conclusions independently. I have since found that they are in entire agreement with the earlier work of Funke,[14] Carl Meeh,[15] Quetelet [16] and all other investigators in this field. They worked

*Four Groups Into Which Surface Area Proportions Fall*

| Group | Surface Area Proportions | Actual Surface Areas | Measurements | |
|---|---|---|---|---|
| | | | Lengths | Circumferences |
| 1 | Normal | Normal<br>Small<br>Normal<br>(Male hirsuties; facial, extremities and escutcheon) | Normal<br>Small<br>Normal | Normal<br>Small<br>Normal |
| 2 | Trunk small (34%); creasing distal to trunk | Trunk small; hands and feet large | Increased | Decreased |
| 3 | Trunk large (to 48%); head small; hands and feet small | Trunk large (upper, shoulder girdle obesity) | Decreased | Increased |
| 4 | Thighs large | Thighs large (lower, pelvic girdle obesity) | Decreased | Increased |

with fewer cases, but far more laboriously, as they did not have the benefit of the Du Bois linear method.

## NEW DATA ON FEMALE CONSTITUTIONAL INFERTILITY AND SEVERE AMENORRHEA GROUPED ON THE BASIS OF SURFACE AREA PROPORTIONS AND ASSOCIATED DATA

On the basis of surface area proportions, the cases studied fall into four groups. A subgroup is distinguished by means of the associated data, i. e., actual surface areas and direct measurements (accompanying table).

12. Berkow, S. G.: Disturbed Surface Area Proportions in a Case of Suspected Ovarian Hyperfunction, J. A. M. A. **88**:1953 (June 18) 1927.

13. Unpublished investigations by me at Montefiore Hospital, New York.

14. Funke: Moleschotts Untersuchung, Naturlehre **4**:36, 1858.

15. Meeh, Carl: Oberflüchenmässungen des menschlichen Körpers, Ztschr. f. Biol. **15**:425, 1879.

16. Quetelet: Des proportion du corps humain, Bull. Acad. roy. d. sc. **15**:580, 1870.

*Group 1 (Eumorphic—Fifty-four Cases).*—The proportions are within the range encountered in normal adult females and also conform to the proportions of a small control group (ten) measured in the contraceptive clinic at Mount Sinai Hospital. For these reasons and because the configuration that yielded these proportions seemed "right" to the unaided view, group 1 is considered eumorphic and its proportions "normal."

However, this group is not uniform as to associated physical data or as to associated symptoms. One subgroup is distinguished (three cases) in which the total surface of the body is remarkably small. The actual areas of the parts and the lengths and circumference by actual measurement are small, but normal ratios are preserved. These women were, of course, short (from 4 feet, 10¼ inches to 4 feet, 11 inches); their weight varied from 112 to 124 pounds (50.8 to 56.2 Kg.) Two of

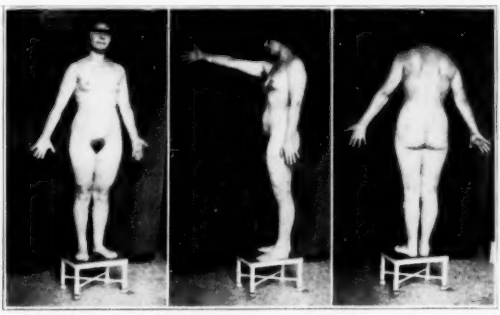

Fig. 2.—E. A., group 1, subgroup 1. The proportions are normal, the actual surfaces are small, and the measurements are small.

the women (aged 26 and 27) had never menstruated, and the third had menstruated four times in the past five years. Secondary sex characteristics were present. The genital organs, particularly the cervix and the body of the uterus, were extremely hypoplastic. In two the sella turcica appeared smaller than normal, and in one there was marked bridging between the anterior and the posterior clinoid process. In all three cases, the female sex hormone was absent from the blood, and in only one was it found in the urine.

A second subgroup (six cases) is distinguished by the masculine character and distribution of hirsuties. This subgroup is included for purposes of classification, although it is not distinguished by the surface area proportions or the associated data of that method. These women were a little taller than those of the first subgroup (from 5 feet, ¾ inch to 5 feet, 2 inches), and their weight was correspondingly greater. The total surface of the body averaged about 1,000 sq. cm. more than

that in the first subgroup. Menstruation was regular in one case, habitually delayed in three cases, and in two cases the patients had been amenorrheic as long as one year. The breasts were large and flabby or had flat nipples. The symphysis pubis was high and thick. The distinguishing characteristic was the male escutcheon and the presence of coarse hairs on the face and extremities, especially the lower extremities. The uterus was small, retroverted or retroflexed, and one of the women had a uterus didelphys and a double vagina. Roentgenograms of the sella turcica were negative. The basal metabolism was minus 12 per

Fig. 3.—M. R., group 2.

cent in one case, and minus 27 and minus 40 per cent in one other case; it was normal in the other cases.

*Group 2—(Two Cases).*—In these two cases the proportions of the trunk were very small (34 per cent and 34.3 per cent), whereas those of the head and the extremities were relatively large. Bichat called this type the hypovegetative or animal type ("the morphological differentiation and the animal system preponderate over the total mass and the vegetative system"—Pende), and Viola termed it the microsplanchnic type. This type of configuration is also called the longitypical, dolichomorphic, hyperevolute and, I believe, eunuchoid. The parts farthest from the trunk have the greatest increase in their proportions. Thus, the hands are large for the arms; the feet are large for the legs, and the legs are large for the thighs. The actual surface of the head and

extremities is not large. The actual measurements show an increase in the lengths and a decrease in the circumferences as compared to all groups. They show that the disproportions are due to increases in length.

Both of these women had primary amenorrhea (aged 26 and 18). They were 5 feet, 5½ inches and 5 feet, 3½ inches, respectively, in height, and weighed 113 and 117 pounds (51.3 and 53.1 Kg.). One had male breasts; the other had small breasts with supererogatory nipples. The latter patient had a total absence of pubic hair and no hair in the axillae, but the hair covering her scalp was fine, long and abundant.

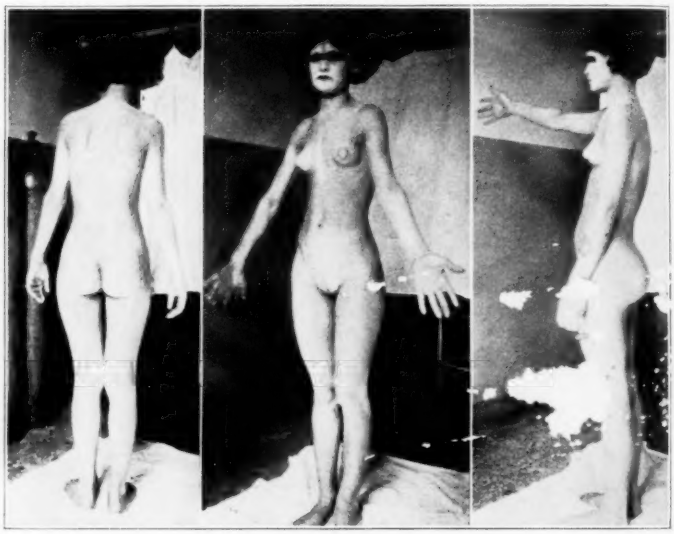

Fig. 4.—J. C., group 2.

The genitals were infantile. The female sex hormone showed a monthly cycle in one case; its presence had not been reported in the other case. Roentgenograms of the sellae turcicae showed them to be normal in size and contour. The basal metabolisms were normal.

*Group 3—(Seven Cases).*—In this group the proportions of the trunk are the greatest. All of the other proportions are small, becoming smaller in the parts distal to the trunk. The average proportions are: head, 5.5 per cent; trunk, 45.5 per cent (limits, 43.7 and 48.4 per cent); arms, 12.2 per cent; hands, 3.7 per cent; thighs, 17.7 per cent; legs, 9.9 per cent; feet, 5.1 per cent. The women in this group would be described as brachymorphic, hypervegetative (from the fact that the

trunk contains the organs of vegetation), hypo-evolute (not so from the surface area proportions) and of the Fröhlich type.

Of the actual surfaces, that of the trunk is outstandingly great (average, 9,113 sq. cm.), compared to other groups. The other surfaces correspond to those of other groups. They are small only when compared to the total surface of the body, the enormous surface of the trunk or the body weight.

Of the actual measurements, *M*, *N* and *Q* (fig. 1) are large, particularly *M* and *N*. The circumferences of the extremities are large near the trunk, particularly when compared to the length.

In this group the women were short (average, 4 feet, 10 inches), and stout (average weight, 184 pounds [83.5 Kg.]). On inspection, the

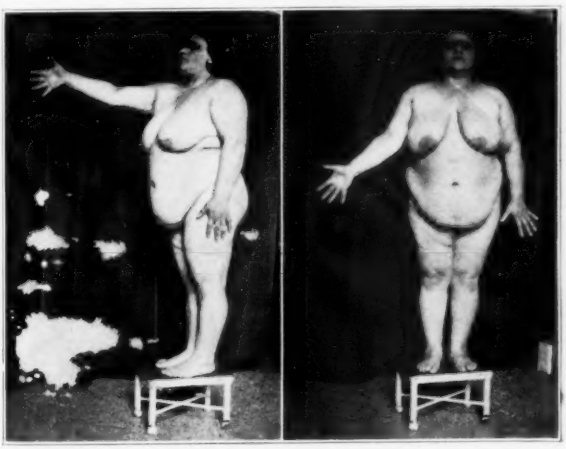

Fig. 5.—R. M., group 3.

obesity was chiefly of the trunk and upper (shoulder) girdle variety. This was best seen from the posterior aspect. Secondary sex characteristics were present. The breasts were large and flabby. The growth of hair was normal, or with the male type of escutcheon.

The menses were irregular and habitually delayed in three cases; in one patient menstruation occurred about once a year; two patients had been amenorrheic for one and a half years, and one had not menstruated in fifteen years.

Pelvic examination gave negative results or showed moderate genital hypoplasia.

In one of the women (J. J., fig. 6) there was positive evidence of a pituitary tumor, for which the patient was treated by operation and deep roentgen therapy at the Mount Sinai Hospital. At the time of

writing this article, roentgen examination showed the operative defect in the floor of the sella turcica. In all other cases, roentgen examination did not demonstrate any definite abnormality of the sella turcica, as to size and contour. Examination of the eyes, the fundi, the visual fields and color vision gave negative results. The carbohydrate metabolism was high in only one case (J. J.). The basal metabolism varied between — 12 and + 9 per cent.

*Group 4—(Six Cases).*—In this group the women are also short and stout. Like the women in the preceding group, they would be described as brachymorphic, hypervegetative and hypo-evolute. In addi-

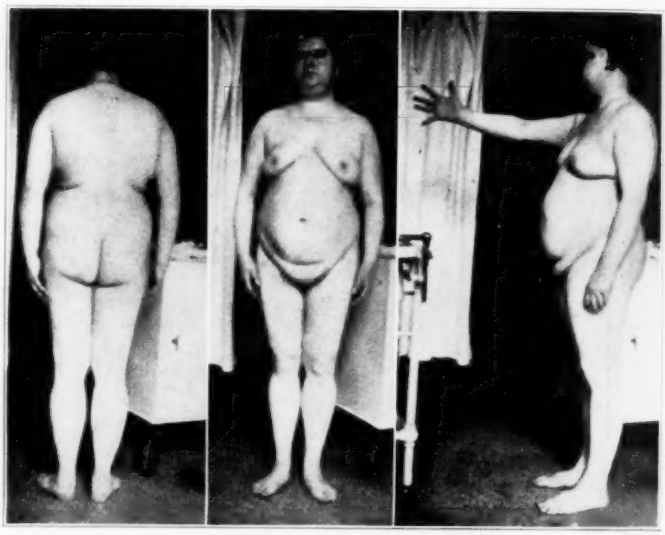

Fig. 6.—J. J., group 3. There was a pituitary tumor.

tion to a large trunk, the women in this group possess heavy lower extremities and the obesity is chiefly of the lower (pelvic) girdle type.

The surface area proportion of the trunk is large, but is less than that in group 3. The proportions of the thighs, legs and feet are larger than in the preceding group and are within the range of my norm. The surface area proportions of the head, arms and hands are as in group 3.

On comparison of the actual surfaces with those in group 3, that of the trunk is considerably less in this group (average, 7,625 sq. cm.); the surfaces of the thigh and the legs are similar to those of the preceding group; the surfaces of the feet are larger than in group 3.

Of the three circumference measurements *M*, *N* and *Q* (fig. 1), the last is greatest in every instance in this group, whereas in group 3, *N*

is the greatest measurement. Only $Q$ is as great in this group as in group 3; $M$ and $N$ are less.

The average height of the women in this group was 5 feet, 2⅞ inches; the average weight, 174 pounds (78.9 Kg.). In four of the six women the gain in weight had taken place soon after marriage. Three women gained from 40 to 50 pounds (18.1 to 22.7 Kg.) each within two years after marriage.

These women showed a tendency toward hirsuties. The pubic hair was more male than female in distribution. The breasts were well developed; in one instance, there was marked asymmetry, the left breast being infantile, the right normal. The pubic arch was high and heavy.

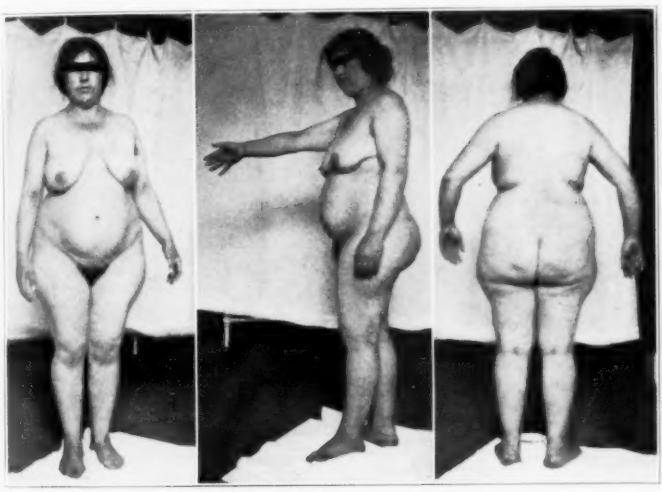

Fig. 7.—M. C., group 4.

Four women were described as masculine in appearance; two as feminine. The "masculine type" of women had heavy superciliary ridges, rather coarse features and darker coloring of the skin.

Severe grades of amenorrhea are met in this group, from irregular menses about every five or six weeks to amenorrhea of three and one-half years' duration.

Pelvic examination revealed moderate to marked hypoplasia.

Studies of the female sex hormone were conducted in three cases. One patient had a subthreshold cycle, and in a second the female sex hormone was absent (R. L., aged 25, had been amenorrheic for three and one-half years). In another case the Rubin test demonstrated patency of the fallopian tubes, but without tubal contractions. At 10 pounds

of pressure, the column of mercury rose to 108 and gradually dropped to 80; fluoroscopy showed a subphrenic pneumoperitoneum (Dr. Mintz). The basal metabolism was within normal limits. The sugar tolerance was normal. No enlargement of the pituitary gland was shown by the x-rays, and the fundi, visual fields and color vision were normal in every case.

## COMMENT AND SUMMARY

An anthropometric and clinical study of sixty-nine "constitutionally sterile" women has been presented. It is noteworthy that male responsibility was eliminated solely on the number, motility and shape of sper-

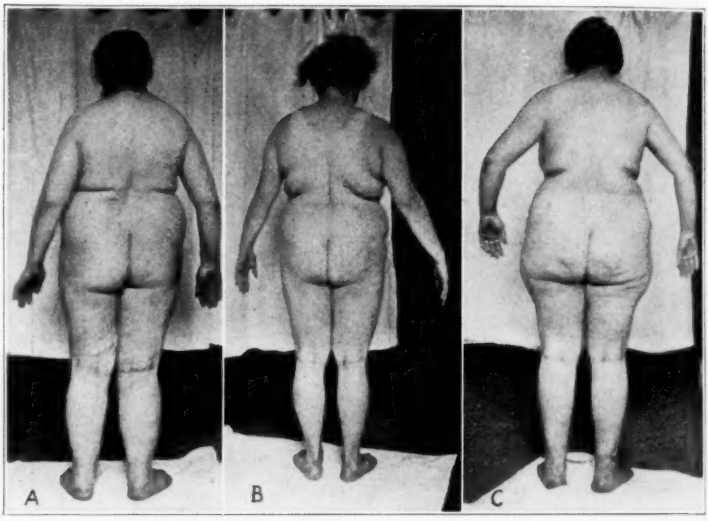


Fig. 8.—*A* shows generalized obesity in an acromegalic woman; *B*, upper (shoulder) girdle obesity (group 3); *C*, lower (pelvic) girdle obesity (group 4).

matozoa in postcoital specimens. Constitutional factors in the males, which may, conceivably, affect the quality or potency of the spermatozoa, were not included in this investigation. The objection may therefore be raised that having failed to establish a mechanical cause in either the female or in the spermatozoa, the blame has been placed arbitrarily on the woman's constitution. This criticism has some merit. A constitutional study of the male partners is greatly to be desired. On the other hand, when abnormal configuration of the body and other endocrine stigmas are demonstrated in the female, it is fair to assume that the responsibility does rest largely with her.

On the basis of the surface area proportions, four groups were differentiated, of which three are considered abnormal. In the normally proportioned group, one subgroup was distinguished by its small actual surfaces and small measurements. Menstruation, secondary sex characteristics, pelvic examination and laboratory observations were found

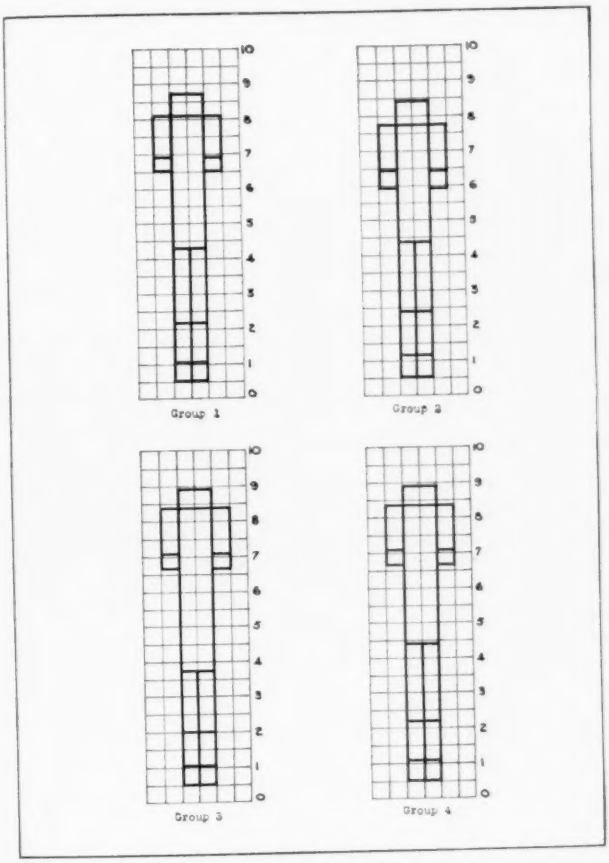


Fig. 9.—A graphic presentation of the surface area proportions in the four groups. The figures are drawn to scale.

to vary less within the groups than between the groups; however, the influence of various glands, to different degrees, was seen in each group. It has not been possible to introduce all evidence against the derangement of the dominant gland in each group. To uncover a little more the culpability of the dominant gland, it would be necessary to intro-

duce further nonsterile cases for comparison. A number of such cases of patients with menorrhagia, acromegalia, hyperthyroidism and hypothyroidism, are available. For the sake of lucidity, they are kept for a later presentation.

With very few cases in each group and each group complicated, to some extent, by a different gland and by a different degree of glandular influence, the wisdom of being categorical may be questioned. It must be remembered that the field of human constitution is a terrain of "many signs and few guide-posts." Any direction, however vague, may prove helpful. Furthermore, this classification is considered, to change the metaphor somewhat, not as a permanent framework, but as a preliminary sketch.

The cases have the further advantage of a thorough work-up. For this credit belongs to the staffs of the endocrine and sterility clinics and to the laboratory and the x-ray and eye services.

The more general object of the study, to determine the clinical availability of the surface area proportions as a means of anthropometric differentiation, seems to have been fully attained. The study has been carried on in active clinics within a narrow allotment of time. The usual routine was not interfered with. Without special instruments and by means of simple arithmetic, a mathematical formula has been reached which is complete in itself and is expressive of certain fundamentals concerning the configuration of the body. The value of this expression can be ascertained only through further study. The greatest need at present is to establish normal standards of height-weight, sex and the stage of physiologic development considered.

# INFLAMMATION

## A PROTECTIVE MECHANISM *

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BOSTON

Although most pathologists are agreed as to the general character of inflammation, various definitions of this fundamental pathologic process have been offered. Some define inflammation merely as the reaction of tissues to injury. Others, following the lead of Cohnheim, define it as the reaction affecting specifically the wall of blood vessels after injury, i. e., the increased permeability that allows the escape of plasma and blood corpuscles into the surrounding tissue. By some, notably Cohnheim [1] and Adami,[2] inflammation is viewed as a process adapted to reduce the harmful consequences of an injury; Metchnikoff, Marchand, and Councilman regarded it solely as a reaction excited by the presence of something injurious to the tissue. Opie [3] defined it as a process by means of which cells and serum accumulate about an injurious substance and tend to remove or destroy it. In the course of this presentation, an attempt will be made to give evidence showing that before and during its removal or destruction, the injurious substance is circumscribed and fixed in situ by the inflammatory reaction.

The process of inflammation, from this point of view, does not include the repair or regenerative changes of healing that follow the inflammatory reaction.

The cardinal symptoms of inflammation (heat, pain, redness and swelling) are perhaps best illustrated by the ordinary boil or by the lesion of erysipelas. The etymology of the word indicates that earlier writers attached primary significance to the increased heat of the inflamed part. In an inflamed area, the normal functional equilibrium between cells, intercellular fluids and blood is doubtless profoundly modified. Local physiologic changes are involved affecting the permeability of

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* A part of this discussion was presented before the Biological Seminar of Princeton University, March 14, 1930.

* From the Henry Phipps Institute of the University of Pennsylvania and the Department of Pathology of the Harvard Medical School.

1. Cohnheim, J.: Virchows Arch. f. path. Anat. **40**:1, 1867.

2. Adami, G. J.: Inflammation, London, Macmillan and Company, 1909.

3. Opie, E. L.: Inflammation, Arch. Int. Med. **5**:541 (June) 1910; J. Immunol. **17**:329, 1929.

capillaries, the rate of blood flow and the balance of body fluids. Increase of capillary permeability is shown by local edema. The proteins of the plasma to a varying extent pass out into the tissue spaces, disturbing, doubtless, the osmotic relationship between tissue fluids and blood plasma. About thirty years ago, Adler and Meltzer [4] concluded that the passage of fluids from tissue spaces into lymphatics probably depends on osmosis, perhaps assisted to some extent by filtration. Starling [5] pointed out that capillary filtration is the resultant of two forces: capillary pressure on the one hand and the osmotic pressure exerted by the plasma colloids on the other. Recently this conception has been confirmed experimentally by the work of Landis [6] who showed by measuring directly intracapillary pressure that the rate of filtration depends on the difference between capillary pressure and the osmotic pressure of plasma colloids. By this direct method he proved that whereas filtration occurs at the arterial end of capillaries, absorption from tissue spaces takes place at the venous end. The normal filtration equilibrium of the capillary wall is modified in inflammation by the passage of plasma proteins into the tissue spaces. If the passage of lymph from tissue spaces into afferent lymphatic vessels depends largely on an osmotic equilibrium, it is probable that the accumulation of plasma proteins in the tissue spaces will modify and retard the flow of lymph into the afferent lymphatic vessels. Schade and Menschel [7] found that in inflamed areas, especially those with suppuration, the accumulation of products of disintegration of the tissues may become so great that the osmotic pressure is raised as high as eleven atmospheres. An inflamed area can be considered as shunted off from the rest of the organism. It has its own metabolism, its own hydrogen ion concentration and, as was just pointed out, its own modified circulation.

### FIXATION OF FOREIGN SUBSTANCES AT THE SITE OF INFLAMMATION

Throughout the remainder of this discussion, one phase of the reaction will be emphasized, i.e., the fixation of foreign substances by the inflammatory process. This is a function that is evidently of great importance as a mechanism of protection to the organism as a whole.

The dissemination of foreign substances from the site of injection into the lymphatics and the blood stream has been studied by various investigators. Muscatello [8] showed that carmine and various other

4. Adler, I., and Meltzer, S. G.: J. Exper. Med. **1**:482, 1896.
5. Starling, E. H.: J. Physiol. **19**:312, 1895-1896.
6. Landis, E. M.: Am. J. Physiol. **81**:124, 1927.
7. Schade, H., and Menschel, H.: Ztschr. f. klin. Med. **96**:279, 1923.
8. Muscatello, G.: Virchows Arch. f. path. Anat. **142**:327, 1895.

inert particles when injected into the peritoneal cavity reach the anterior mediastinal lymph nodes rapidly. Buxton [9] found that when typhoid bacilli were injected into the peritoneal cavity they appeared in the blood stream in great numbers within a few minutes. Wells and Johnstone [10] demonstrated that the absorption from the peritoneal cavity takes place through lymphatic vessels.

Within recent years, evidence has accumulated indicating that an inflammatory reaction at the site of injection might be a factor in delaying the passage of foreign substances into the circulating blood. Noetzel [11] demonstrated that the injection of bacteria (*B. pyocyaneus*) into the knee joint of rabbits was followed by a rapid dissemination of the micro-organisms, which could be recovered five or ten minutes later from the inguinal, crural and lumbar lymph glands. Pawlowsky [12] repeated Noetzel's experiment and also injected staphylococci into a knee joint that had been previously inflamed by a sterile irritant such as turpentine or alcohol. The dissemination of the bacteria was either inhibited or wholly prevented by the acute inflammatory reaction. These observations have been confirmed. Opie [13] showed that a foreign protein injected into the skin of an immunized animal is fixed at the site of injection, where the contact of antigen and antibody causes an acute inflammatory reaction (phenomenon of Arthus). In normal animals, on the contrary, foreign proteins when injected into the skin produced little if any inflammatory reaction and readily penetrated into the blood stream. Recently the same investigator demonstrated that acute inflammation of the peritoneal cavity caused by a sterile irritant, aleuronat, retards the rush of injected hemolytic streptococci from the peritoneal cavity into the circulating blood stream. After the inflammation has lasted twenty-four hours, the passage of bacteria from the peritoneal cavity is completely prevented.

Gay [14] and his collaborators studied the changes in resistance to intrapleural inoculation of streptococci after a sterile inflammation had been previously caused by various irritants. They contended that the increased resistance to the pathogenic micro-organism results from the accumulation of clasmatocytes. This interpretation was recently questioned by Opie,[15] who maintained that there are as yet no data that will

9. Buxton, B. H.: J. M. Research **16**:17, 1907.
10. Wells, H. G., and Johnstone, O. P.: J. Infect. Dis. **4**:582, 1907.
11. Noetzel, W.: Beitr. z. klin. Chir. **51**:740, 1906.
12. Pawlowsky, A. D.: Ztschr. f. Hyg. u. Infektionskr. **62**:433, 1909.
13. Opie, E. L.: J. Immunol. **9**:259, 1924; J. Exper. Med. **39**:659, 1924.
14. Gay, F. P., and Morrison, L. F.: J. Infect. Dis. **33**:338, 1923.
15. Opie (footnote 3, second reference).

determine the rôle of polymorphonuclear leukocytes, mononuclear cells, serum or, indeed, increased permeability of blood vessels in overcoming the injurious effects of sterile irritants or of bacteria.

During the past two years I have been studying the behavior of foreign substances injected into an inflamed area, by direct observations of the tributary lymphatic nodes and vessels draining that area. After some preliminary experimentation with nucleated corpuscles in fowls, a vital dye, trypan blue, was tried and found to be satisfactory.[16] If trypan blue is injected into the normal subcutaneous tissue of the fore leg of a rabbit, within from twenty to thirty minutes the dye stains the tributary afferent lymphatic vessels, the lymph node and the efferent lymphatic. If, on the other hand, the dye is injected into a similar area in which an inflammatory reaction has been produced some time before by a sterile irritant, the dye does not appear in the tributary lymphatics; the afferent lymphatics, the lymph node and the efferent lymphatic vessel remain colorless. The dye is evidently retained in the inflamed area. The fixation of the dye takes place very soon after the injection of the irritant; this reaction was observed in some instances when the dye had been injected thirty minutes after injection of the irritant.

Since trypan blue tends to remain in situ when injected directly into the inflamed area, an attempt was made, at the suggestion of Dr. Opie, to determine whether the dye injected into the blood stream would accumulate at the site of inflammation. MacCurdy and Evans[17] pointed out in 1912 that the normal brain and cord always remain free from dye injected intravenously, but that areas of damage, such as softening or inflammation, become deeply stained.

Other investigators have confirmed the early observations of MacCurdy and Evans. It was found that trypan blue introduced into the circulating blood rapidly entered the site of inflammation, staining the tissue deeply, and that it did not readily drain away through the tributary lymphatic vessels. It was further observed that the longer the interval of time between the injection of the irritant and that of the dye, the more complete was its retention, less of the dye diffusing to the regional lymph node. Thus, there is not only a rapid accumulation but also a fixation of dye from the blood stream in the inflamed area.

It is well known that the retrosternal lymph nodes of the anterior mediastinum drain the peritoneal cavity. If trypan blue is injected into a normal peritoneal cavity, the retrosternal lymph nodes are within a short time deeply stained with the dye; but if the dye is injected into a peritoneal cavity in which an inflammatory reaction has been set

16. Menkin, V.: J. Exper. Med. **50**:171, 1929.

17. MacCurdy, J. T., and Evans, H. M.: Berl. klin. Wchnschr. **49**:1695, 1912.

up by a sterile irritant such as aleuronat, the dye is wholly or partly prevented from reaching the retrosternal lymphatic nodes. Consequently, from these studies the following principle has been established: A vital dye, trypan blue, injected into the circulating blood stream rapidly accumulates in an inflamed area and is fixed there, so that it fails to appear in the tributary lymphatics draining the area.

The accumulation in inflamed tissue of the dye when introduced into the blood stream is doubtless influenced by increased capillary permeability, which is part of the inflammatory reaction.[18] We have been able to secure quantitative data by studying directly the change in the concentration of the dye in the blood stream both in the inflamed and in the normal mesentery of the frog.

After intraventricular injection of the dye the change in concentration of trypan blue within the capillaries may be estimated by a colorimetric method. When the logarithms of the concentrations of dye within the capillary are plotted against time, a straight line is obtained denoting an exponential type of relationship. The equations obtained by the method of least squares for both the normal and the inflamed areas were of the following type:

$$y = Ae^{-ax}$$

The actual equations found were:

(1) In the normal peritoneal cavity: $y = 7.63e^{-0.24x}$

(2) In the inflamed peritoneal cavity: $y = 6.9e^{-0.42x}$

$y$ represents the concentration of dye in the capillaries as estimated by comparison with the nearest standard on the colorimetric scale and $x$ stands for the time in minutes after the intraventricular injection of the dye; $a$ represents the slope of the curve. In the equation for the control experiments, $a$ was found to equal 0.24 while in the equation for the concentration of dye in the capillaries of the inflamed peritoneal cavity, $a$ equaled 0.42. Since $a$ is an index of the slope and consequently of the rate of change of concentration of the dye, it is clear that the rate of fall of concentration of trypan blue in the capillaries of an inflamed area is almost twice as rapid as in the capillaries of the normal mesentery. The dye obviously diffused outward into the extracapillary spaces, as can be seen by direct observation and, of course, by the fact that the dye stains the cells of the extracapillary spaces. This does not necessarily mean that the fall of concentration in dye within the capillaries is an exact measure of the amount of dye that passes through their walls, for it is conceivable that there may be other factors involved. However, in view of our previous studies, showing that trypan blue injected intravenously rapidly passes into an inflamed area, it is believed that the increased rate of fall of concentration is a measure of increased passage of dye through the capillary wall.

Landis showed that capillaries injured by alcohol and mercuric chloride are permeable to the plasma colloids and approximately seven times more permeable to fluids than the normal capillary wall. It seems probable that similarly the inflammatory irritant may have a direct toxic effect on the capillary walls and, by increasing their permeability, may cause a fall in the osmotic pressure of the plasma colloids. Such

18. Menkin, V., and Menkin, M. F.: J. Exper. Med. **51**:285, 1930.

direct injury would result in an increased rate of filtration of the dye in the inflamed area and would account for the increased rate of fall in concentration of the dye within the capillaries. Landis,[19] however, recently demonstrated that when a wheal is formed on the skin by freezing or when a blister is caused by the application of cantharides plaster, the average capillary pressure at the point of injury rises appreciably. This factor in addition to increased capillary permeability will also increase the filtration of substances into the extracapillary spaces.

Further studies were then undertaken to see whether a metal would, like the dye, be fixed in situ by the inflammatory reaction.[20] Iron was selected because of the ease of detecting this metal in tissues qualitatively by the prussian blue reaction. When colloidal iron or ferric chloride is injected into the normal peritoneal cavity of rabbits, it rapidly accumulates in the retrosternal lymph nodes, as is shown by the prussian blue reaction, but it fails to reach these lymph nodes when it is injected into a peritoneal cavity in which inflammation has been caused either by aleuronat or by *Staphylococcus aureus*. Quantitative studies by the method of Kennedy [21] of the iron content of these lymph nodes in animals injected intraperitoneally with ferric chloride revealed 56.7 per cent more metal in the nodes of the animals with normal peritoneal cavity than in those with inflamed peritoneal cavity. Experiments were then performed to demonstrate the accumulation of the metal in inflamed areas when ferric chloride was injected into the circulating blood stream. Acute inflammatory reactions of from six to seven hours in duration were obtained by the injection of *Staphylococcus aureus* into the skin of the abdomen of rabbits. Such acute inflamed dermal areas do not themselves give the prussian blue reaction, but when ferric chloride is injected intravenously the metal becomes demonstrable in these areas by the qualitative tests. Quantitative determinations show, in inflamed areas of the skin of noninjected animals, as an average figure 9.7 mg. of iron per hundred grams of dry tissue as compared with 16.2 mg. in the inflamed areas of the skin of animals injected intravenously with ferric chloride, or an increase of 67 per cent in iron content after the introduction of the ferric salt. The average iron content of normal areas of the skin in injected animals is 10.4 mg. as compared with 8.4 mg. in noninjected animals, showing an increase of 23.8 per cent as a result of injecting the metallic salt. Thus about three times more metal accumulates in inflamed than in normal areas of the skin. These observations show

19. Landis, E. M.: Heart **15**:209, 1930.

20. Menkin, V.: J. Exper. Med. **51**:879, 1930.

21. Kennedy, R. P.: J. Biol. Chem. **74**:385, 1927.

that iron, like trypan blue, accumulates in an inflamed area when injected intravenously and is fixed there by the inflammatory reaction.

These studies may have clinical applications. It is conceivable that by the accumulation of dye, iron or other materials in an inflamed area, the character or course of development of the inflammatory reaction may be altered.

As previously mentioned, Opie [13] showed that foreign protein injected into the skin of an actively immunized animal is fixed at the site of injection where the contact of antigen and antibody causes an acute inflammatory reaction (phenomenon of Arthus). In view of this work on immunized animals and of the results obtained with trypan blue and iron, experiments were undertaken to determine whether a readily identified foreign protein such as horse serum injected into an area of inflammation caused by either bacteria or a sterile irritant would also be retained in situ by the inflammatory reaction.[22]

Horse serum was injected into the peritoneal cavity of normal rabbits and of rabbits that had previously been given an intraperitoneal injection of an inflammatory irritant. The presence of the foreign protein was tested by the precipitin reaction on blood samples removed at varying intervals from the heart. It was found that horse serum injected into an inflamed peritoneal cavity penetrates into the blood stream less rapidly than when introduced into the normal cavity. Furthermore, it was noted that when the foreign protein is injected into a cutaneous inflammatory area, it is held in situ for a longer period than when injected into an inflamed peritoneal cavity.

These experiments show that, like trypan blue and iron, complex foreign proteins such as are found in horse serum when injected into an inflamed area (caused in Opie's experiments by the contact of antigen and antibody and in the present experiments by a sterile irritant) are held fixed by the inflammatory reaction.

With the demonstration that the penetration of horse serum into the blood stream is delayed at the site of inflammation, the attempt was made to determine whether, as with trypan blue and ferric chloride previously studied, horse serum injected into the circulating blood stream would accumulate in inflamed areas to a greater extent than in normal tissue.

Areas of cutaneous inflammation were induced by the injection of about 0.2 cc. of a saline suspension of *Staphylococcus aureus* into the skin of the abdomen of rabbits. About three hours later, 10 cc. of horse serum was injected intravenously. The animal was killed when the inflammation was of from five to six hours' duration. Saline extracts obtained from the inflamed areas of the skin and normal

22. Menkin, V.: J. Exper. Med. **52**:201, 1930.

areas of the skin were tested for the presence of horse serum. It was consistently found that a greater concentration of the foreign protein could be recovered from the site of inflammation than from the corresponding normal area of the skin. These results are, therefore, similar to those obtained with trypan blue and with ferric chloride. The accumulation of foreign protein in inflamed tissue is doubtless in part the result of the increased passage of fluid from the circulating blood stream, but the observations previously recorded indicate that its escape from the site of inflammation is retarded.

These observations offered a means of explaining an interesting observation made some years ago by Auer.[23] This investigator showed that if the ear of a rabbit immunized with horse serum is painted with xylene following reinjection of the homologous antigen into the peritoneal cavity, an intense inflammatory reaction followed by necrosis takes place in the affected ear. No such severe reaction was seen when xylene had been applied to the ear of a normal rabbit after a single injection of horse serum.

In view of the observations on the accumulation of foreign protein in inflamed areas, it is highly probable that the reaction in Auer's experiment is simply the result of an accumulation in the inflamed ear of sensitized animals of antigen and antibody from the circulating blood stream. The contact of antigen and antibody in the tissues evidently causes an acute inflammatory reaction, thus intensifying the mild reaction produced by xylene alone. This explanation was verified by the demonstration in several experiments that horse serum from the circulating blood accumulates in greater concentration in the inflamed than in the normal ear.

It is also possible that the phenomenon of focal reaction in tuberculosis may be explained by the foregoing observations. When tuberculin is introduced into the blood stream of an animal with a tuberculous lesion, an intense inflammatory reaction may develop in the lesion. The mechanism of this focal reaction in tuberculosis is not understood. It is conceivable in view of the experiments with horse serum that in a like manner tuberculoprotein from the blood stream may accumulate in the inflamed tuberculous lesion and by its presence there induce a local inflammatory reaction.

Some recent work by Shwartzman[24] described an interesting reaction that occurs when the filtrate of *B. typhosus* is injected into the skin of rabbits. If twenty-four hours later the same filtrate or a filtrate of a nonrelated organism such as the meningococcus is introduced into the blood stream, hemorrhagic necrosis often takes place at

23. Auer, J.: J. Exper. Med. **32**:427, 1920.

24. Shwartzman, G.: J. Exper. Med. **48**:247, 1928.

the site of the injection into the skin. The observations that I have presented on the accumulation and fixation of foreign proteins at the site of inflammation suggest that the intense reaction of the skin following the intravenous injection of bacterial filtrates may be the result of an accumulation of these substances in an area of skin already inflamed, with resulting accentuation of the original cutaneous lesion. The reaction does not necessarily have to take place with all bacterial filtrates or inflammatory irritants. Questions involving degree of capillary permeability and of optimum synergistic action of two irritating substances on one another may modify the final reaction. Conceived from this angle, it is suggested that the phenomenon may be purely a nonspecific reaction resulting from the accumulation of an irritating substance in an inflamed area. Frisch [25] recently demonstrated that this reaction took place in the prepared area of skin if the bacterial filtrate was injected intraperitoneally. When, however, the filtrate had previously been injected several times into the peritoneal cavity, the cutaneous reaction failed to occur when the filtrate was injected intraperitoneally, but not when it was injected intravenously. The failure of the reaction may perhaps be explained in terms of fixation of the bacterial filtrate in a peritoneal cavity inflamed by preliminary injections of the filtrate.

The studies on fixation have recently been extended to include bacteria and particulate matter.[26] The accumulation of bacteria at the site of inflammation from the circulating blood stream may explain the well known localization of bacteria in a locus minoris resistentiae in terms of increased capillary permeability with subsequent accumulation and fixation of bacteria at the point of injury.

After the demonstration that the accumulation of foreign substances from the circulating blood in an inflamed area is doubtless associated with increased capillary permeability, studies were extended in an attempt to determine the mechanism of fixation by the inflammatory reaction.[27]

The leukocytes are probably not a very significant factor in the mechanism of fixation, for two reasons. Histologically, no definite evidence could be obtained of phagocytosed particles in the leukocytes of the inflamed area at a time when fixation of foreign substances was already demonstrable by examining the tributary lymphatics. In the second place, fixation of trypan blue at the site of inflammation was shown to occur as early as thirty minutes after the injection of the

25. Frisch, I. A.: Demonstration of Local Immunity of the Peritoneum by Means of the Schwartzman Phenomenon, Arch. Int. Med. **46**:410 (Sept.) 1930.

26. Menkin, V.: J. Exper. Med. **53**: 647, 1931.

27. Menkin, V.: J. Exper. Med. **53**: 171, 1931.

inflammatory irritant.[16] The occurrence of fixation at this early stage of the inflammatory reaction, when there are as yet relatively few leukocytes present, seems to point toward some other factor responsible for fixation.

A factor which may explain fixation is mechanical obstruction. It is conceivable that a network of fibrin and thrombosed lymphatics at the site of inflammation may arrest the passage of particulate material injected into such an inflamed area. The dissemination of fluids would probably also be retarded by mechanical obstruction of this kind, though probably not as effectively as solid particles which would be more readily caught in a fibrinous network. In this connection it is interesting to note that some years ago Opie [28] shrowed that when cantharidin is administered intramuscularly the flow of lymph through the thoracic duct is at first diminished, but later may be increased. The decrease in the flow of lymph was accompanied by acute edema of the liver and of the gallbladder. This edema was due to plugging by fibrin of the afferent lymphatics and the sinuses of lymph nodes that drain these organs. The observations of Adami [2] are also significant in this connection:

> Even when inflammation (as in pericarditis) affects the whole extent of a serous cavity, the layer of fibrin acts as a protective coat closing the lymphatic "stomata" hindering the free absorption of the morbid material by the lymph and blood vessels, and filtering bacteria out of such fluid as does find its way through to the tissues beneath.

In the endeavor to throw some light on the mechanism involved in fixation, a series of experiments was undertaken to determine whether the inflammatory exudate in itself possessed some property that might facilitate the fixing of foreign substances in the inflamed area.

It was found [27] that when ferric chloride was added directly to the inflammatory exudate, heavy precipitation occurred. The compound formed is presumably a ferric proteinate.[29] When horse serum was added to the exudate and incubated at 37 C. for a short interval of time, coagulation occurred. When, however, trypan blue was added to an inflammatory exudate, no effect was noticed. Yet this vital dye was shown to be definitely held in situ by the inflammatory reaction. The reaction of fixation must be due primarily to some other mechanism than precipitation or coagulation of foreign substances by the inflammatory exudate. As it has been shown, however, that iron compounds are apparently more effectively held by the inflammatory reaction than trypan blue, it is possible that precipitation or coagulation of foreign substances acts as a secondary factor in the mechanism of fixation by preventing rapid dissemination from the site of inflammation.

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28. Opie, E. L.: J. Exper. Med. **16**:831, 1912.
29. Smythe, C. V., and Schmidt, C. L. A.: J. Biol. Chem. **88**: 241, 1930.

Sections were made of the inflamed tissue of rabbits in experiments in which either trypan blue or ferric chloride had been shown to be fixed in situ by the inflammatory process. There is, as a rule, a central area of dense leukocytic infiltration. The intensity of the inflammatory reaction in the immediate neighborhood of veins and arteries is noteworthy. It is to be recalled [16] that when the dye was injected intravenously it would not always penetrate into the central zone of the inflamed area. This is evidently due to thrombosis of the small vessels, for sections of such areas reveal some thrombosed vessels with acute inflammatory changes in the surrounding tissue.

Histologically, there is little evidence of phagocytosed particles of trypan blue or of iron within the leukocytes at a time when retention of these substances at the site of inflammation is clearly demonstrable.

It is of interest to note the meshwork of fibrin that is found usually at the periphery of the zone of dense infiltration (fig. 1). In the same region, careful study reveals many lymphatic vessels which are thrombosed, one of which is illustrated in figure 2. The thrombus is characterized by numerous leukocytes within a delicate fibrinous reticulum. The fact that there are many occluded lymphatics and a dense network of fibrinous strands within tissues that are distended with edema at the site of inflammation supports the view that foreign substances, especially solid particles, such as precipitated iron salts, can disseminate only with difficulty from the inflamed area through the regional lymphatic vessels.

If, as described, the thrombosed lymphatics and the network of fibrin in an acutely inflamed area are instrumental in preventing mechanically the free passage of substances from the site of inflammation, it follows that for the same reason similar substances injected at the periphery of the inflamed area should fail to enter it. To test this hypothesis, the following experiments were conducted at the suggestion of Professor Eugene L. Opie.

An inflammatory reaction was induced in the skin of the abdomen of a rabbit by the use of a bacterial irritant (*Staphylococcus aureus*) or by injecting concentrated broth. After a varying interval of time, trypan blue was injected at the periphery of the inflamed area in from four to six places. In this way the inflamed area became circumscribed by a blue band. In a normal area of skin, similar injections of dye were made to serve as control. Several hours later, the inflamed area within the original circumscribed blue band showed no trace of dye whereas the normal area of skin was diffusely blue. The dye had evidently failed to penetrate into the site of inflammation when injected at its periphery, owing to the presence of thrombosed lymphatics and of a fine network of fibrin in the tissue spaces. Experiments of the same type reproduced in frogs yielded similar results.

Fig. 1.—Site of inflammation, showing network of fibrin in the subcutaneous tissue of a rabbit. Trypan blue was injected directly into this area and was shown to be fixed in situ. Low power magnification. (From the Journal of Experimental Medicine).

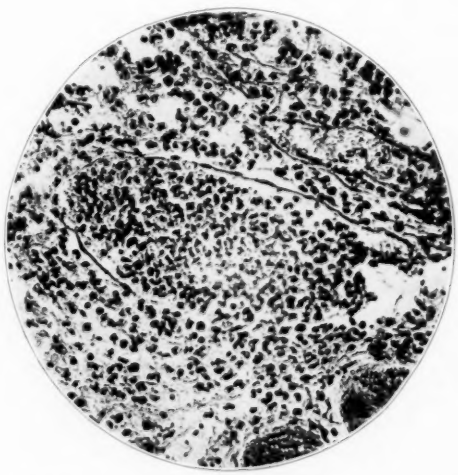

Fig. 2.—Site of inflammation. Same section as in figure 1, but in a different field. A lymphatic occluded by a large thrombus. High dry magnification. (From the Journal of Experimental Medicine.)

Direct observation with a binocular dissecting microscope demonstrated [30] that in frogs the failure of the dye to penetrate into an inflamed area was evidently due to the mechanical obstruction of lymphatic vessels by blood clots. These observations have recently been confirmed with bacteria.[26]

Fixation of foreign substances by the inflammatory reaction is therefore primarily due to mechanical obstruction caused by a fine network of fibrin and by thrombosed lymphatics at the site of inflammation. Further experiments are being conducted to determine the relation between exudation from blood vessels and change in lymph flow from the site of inflammation. This phase of the problem still requires further investigation.

The reaction of fixation occurs extremely early in the inflammatory process. In some experiments,[16] it was found that as short an interval as thirty minutes after the injection of an inflammatory irritant was sufficient to prevent the dissemination of a vital dye from the site of inflammation. This prompt and early reaction in the development of the inflammatory process circumscribes the irritating substance and allows a definite period of time for the leukocytes to assemble for the purpose of phagocytosis. Through this delicate nonspecific mechanism of fixation, the organism is protected at the expense of local injury.

30. Menkin, V.: J. Exper. Med. **53**:179, 1931.

# MECHANISM OF PRODUCTION OF SUBAURICULAR BEATS BY DIGITALIS BODIES*

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While observing continuously the string of the electrocardiograph in an experiment on animals, after digitalis had been injected, we noted that a normal sinus rhythm was present when the animal was quiet, and that ventricular ectopic beats appeared temporarily after a struggle. This phenomenon recurred many times in the same animal. When the dose was increased, ectopic beats appeared and were uninfluenced by struggling. In another experiment, ectopic beats appeared spontaneously after an injection of digitalis and disappeared when the animal struggled. Struggling obviously calls forth a variety of agencies acting on the heart. Some of these agencies depend on the connection of the heart with the central nervous system, such as reflexes from various organs; others may produce their effects on the heart even after it has been isolated from the central nervous system, such as dynamic changes in the circulation or chemical factors in the blood, for example, epinephrine acting on the sympathetic nerve endings in the heart. The present investigation was undertaken to extend the preliminary observations and to study some of the factors involved in the production and abolition of ectopic beats by the struggling of an animal under the influence of digitalis.

## REVIEW OF THE LITERATURE

Patients under the influence of digitalis may not show premature ventricular contractions during rest, but frequently they show a considerable number in the period of recovery after exercise. Spontaneous premature ventricular contractions in patients are known often to diminish in number or to disappear during exercise, only to reappear in greater numbers during the period of slowing of the sinus rate following exercise.

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In the course of an electrocardiographic investigation [1] of various digitalis bodies, a result was obtained in early experiments that seemed to be at variance with those obtained by other investigators. Robinson and Wilson [2] found that digitalis injected intravenously in several doses into the cat (10 per cent of the calculated fatal dose every ten minutes) called forth ventricular ectopic beats after the injection of approximately 70 per cent of the fatal dose. The percentages for the different animals of this group were fairly uniform, a very low figure being exceptional (70, 77, 72, 87.5, 78, 100, 28, 70, 71.5 and 64). With a specimen of tincture of digitalis which we employed in the same way, ectopic beats appeared much earlier in the first seven experiments, after about 45 per cent of the fatal dose had been administered, a very high figure being the exception in this series (44, 29, 90, 30, 42, 53 and 30). In a larger series of experiments with this specimen of the drug, some higher figures were obtained, so that in the entire group of sixteen experiments, ectopic beats appeared after an average of about 60 per cent of the fatal dose had been injected. There were two important differences between our experiments and those of Robinson and Wilson. First, we did not employ the same specimen of the drug. Second, they used ether anesthesia, and our experiments were performed without general anesthesia.

Halsey [3] found that crystalline strophanthin injected intravenously into unanesthetized dogs frequently called forth ventricular ectopic beats after the administration of from 20 to 40 per cent of the fatal dose. Gold and Edwards [4] observed that ectopic ventricular beats appeared only after 40 per cent or more of the fatal dose of ouabain had been injected intravenously into dogs anesthetized with ether.

All these observations have this factor in common, namely, that ectopic beats were produced with a smaller percentage of the fatal dose, in both dogs and cats, in those cases in which the animals were not anesthetized by ether during the course of the injections. This suggested that the ether might be the cause of the differences between the results obtained in unanesthetized animals and in those under ether anesthesia, since in the latter condition the animals cannot struggle, and reflexes are depressed.

It has long been known that the extrinsic cardiac nerves play an important part in the action of digitalis on the heart. Pearcy and

1. Gold, H.; Hitzig, W.; Gelfand, B., and Glassman, H.: Am. Heart J. **6**:237, 1930.

2. Robinson, G. C., and Wilson, F. N.: J. Pharmacol. & Exper. Therap. **10**: 491, 1918.

3. Halsey, J. T.: J. Exper. Med. **25**:729, 1917.

4. Gold, H., and Edwards, D. J.: Am. Heart J. **3**:45, 1927.

Howard[5] reported interesting experimental observations on the production of cardiac disturbances reflexly (elevation of the T-wave, decrease in the interval R to end of T and ventricular ectopic beats) in the dog under barbital anesthesia, by stimulation of various peritoneal viscera. They concluded from the experiments that the impulses passed over the sympathetic nerves (visceral afferent nerves to the cord and sympathetic efferent nerves to the heart) and that the vagi were not involved, because vagotomy did not influence the production of the disturbances. In some of these experiments it is probable that a relatively high degree of digitalization had been produced because enough of the drug had been injected at the start to call forth spontaneous ventricular ectopic beats. As we shall presently show, the vagal factor in the production of ectopic beats may be much more in evidence after smaller doses of digitalis. While it may be true that the reflex from the intestine to the heart is mediated directly through the sympathetics, it is probable that the vagus (efferent to the heart) could be shown to exert considerable influence on the production of ventricular ectopic beats through stimulation of abdominal viscera under certain conditions after smaller doses of digitalis.

The part played by the extrinsic cardiac nerves in the reaction of the heart to digitalis has been investigated experimentally in great detail by Rothberger and Winterberg.[6] They administered digitalis bodies to dogs and studied the effects of direct electrical stimulation and paralysis or excision of these nerves on the various cardiac structures. They showed that large doses of digitalis may call forth ventricular ectopic beats spontaneously but that after smaller doses, stimulation of the accelerator nerves may be necessary to produce them. In some cases in which both of these factors are insufficient, the additional stimulation of the vagus will produce them. Rothberger and Winterberg believed that sympathetic stimulation acts directly on the ventricle to increase its rhythmicity, already above normal as the result of the direct action of digitalis, while stimulation of the vagus produces no direct action but supplants a regular sinus rhythm by an idioventricular rhythm through suppression of the sinus pacemaker.

Robinson and Draper[7] reported interesting observations on the production of a subauricular ectopic rhythm by the suppression of the sinus through vagal stimulation in children with organic heart disease in whom there was other evidence of high sympathetic tone.

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5. Pearcy, J. F., and Howard, H.: Am. Heart J. **2**:530, 1927.

6. Rothberger, C. J., and Winterberg, H.: Arch. f. d. ges. Physiol. **150**:217, 1913.

7. Robinson, G. C., and Draper, G.: J. Exper. Med. **15**:14, 1912.

## DETAILS OF THE EXPERIMENTS

Experiments were performed on nineteen cats. The animal was tied on its back on the table. Since only minor operations were necessary, they were all performed with local anesthesia with phenol in oil. The excitement or struggling varied in intensity and in duration but was usually very brief. Sometimes it was spontaneous; at other times it was induced by pinching of the hind leg. The latter procedure did not produce any electrocardiographic changes unless struggling followed. Electrocardiograms were taken, lead II being used. In many cases, the tracing was started before and continued during and after the struggle, in order to record as accurately as possible the various time factors involved. In most cases, the string was observed almost continuously throughout the course of the experiment. Three members of the digitalis group were used: a tincture of digitalis in seven experiments, digitoxin-Merck in six experiments and ouabain in six experiments. All injections were made intravenously in the dilutions described in the previous study.[1] No qualitative differences between these substances were detected with reference to the phenomenon under investigation; hence, for convenience, we shall refer to the results in terms of digitalis alone.

In order to determine the part played by reflexes involving the nervous connection of the heart to the central nervous system, experiments were carried out in animals in which the heart was isolated by severing the vagi in the neck and removing the inferior cervical and stellate ganglions on both sides by dissecting in the neck along the course of the cervical sympathetic trunk. This operation was performed during ether anesthesia, the animal being allowed to recover from the anesthesia during a period of about two hours following the operation before the injection of digitalis was started. At this time, the animal was able to struggle violently, either spontaneously or after stimulation.

From eighteen to thirty-five electrocardiograms were obtained in each experiment. In the accompanying tables and figures typical records are reproduced, illustrating the conditions under which subauricular ectopic beats occur in the two stages in the action of digitalis. The P-P and R-R intervals were determined for the period of rest and at various times after the struggle. Since the record was often taken continuously before, during and after the struggle (in some cases it was necessary to discontinue during the most violent period of the struggle), it was possible to determine changes with considerable precision. No attempt was made to read the intervals to less than 0.01 second. Hence, when rates are referred to as being the same, it is possible that there were slight differences, which were not detectable by this technic.

In speaking of ectopic beats in this paper, only those of subauricular (usually ventricular) origin will be referred to. The intervals between subauricular ectopic beats will be designated r-r and those between normal beats, R-R intervals.

It is not feasible to present in detail the data of any number of the experiments. An intensive analysis of some of the electrocardio-

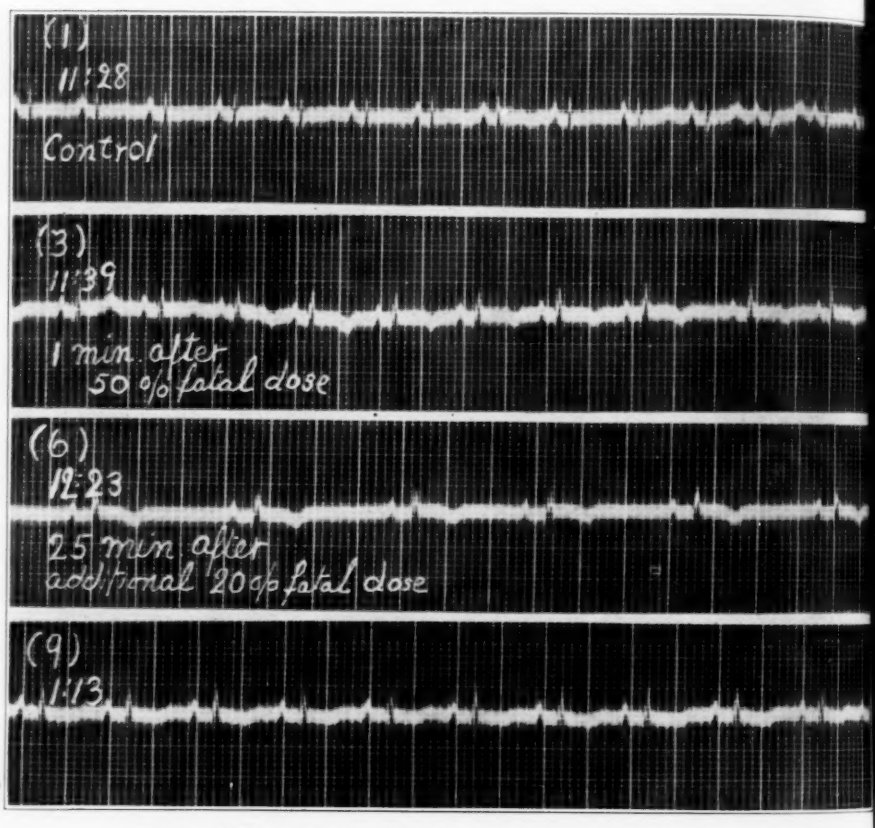


Chart 1.—Marked slowing of the sinus rate after the administration of a small dose of digitalis. Struggling fails to produce ectopic beats.

grams obtained in one experiment is given to show the type of analysis carried out in all the others.

Experiment 1.—*Marked Slowing of the Sinus Rate; Struggle Fails to Produce Ectopic Beats.*—The electrocardiogram of the normal control (chart 1) showed a P-P interval of from 0.29 to 0.33 second and a P-R interval of 0.08 second. Fifty per cent of the average fatal dose of digitalis was injected, and

within one minute the P-P interval became from 0.41 to 0.48 second, the positive T-wave became negative and the P-R interval remained unchanged. After twenty minutes, 20 per cent more was injected, and the record eight minutes later showed a P-P interval of 0.72 second and a P-R interval of 0.11 second. This slow sinus rate did not persist long, as is shown in tracing 9. The record taken twenty-five minutes after the second injection is given in tracing 6. During this period the animal was made to struggle eight times, but no ectopic beats were produced.

TABLE 1.—*Effect of a Struggle on the Production of Ectopic Beats Following the Smaller Dose of Digitalis* *

| Time of Recording | P-P Interval, Seconds | R-R Interval, Seconds |
|---|---|---|
| Immediately before struggle (condition of animal: quiet).. | 0.32 | 0.32 |
| After struggle | — | 0.30 |
| | — | 0.34 |
| One second after struggle | — | 0.39 (R-r) |
| | — | 0.36 (r-r) |
| | — | 0.36 (r-r) |
| | — | 0.34 (r-R) |
| | 0.32 | 0.31 |
| | 0.34 | 0.36 |
| | 0.44 (P-p) | 0.39 (R-t) |
| | 0.36 (p-p) | 0.37 (r-r) |
| | — | 0.36 (r-r) |
| | — | 0.37 (r-R) |
| | 0.32 | 0.32 |
| | 0.33 | 0.32 |
| | 0.35 | 0.35 |
| | 0.40 | 0.39 (R-r) |
| | — | 0.37 (r-r) |
| | — | 0.38 (r-r) |
| | — | 0.38 (r-r) |
| | — | 0.39 (r-r) |
| | 0.32 | 0.36 (r-R) |
| | 0.32 | 0.32 |
| | 0.32 | 0.32 |
| | 0.32 | 0.32 |
| | 0.41 | 0.40 (R-r) |
| | 0.34 | 0.36 (r-R) |
| | 0.36 | 0.36 |
| | 0.34 | 0.35 |
| | 0.37 | 0.37 |
| Tracing two seconds long omitted (no ectopic beats in this record) | | |
| | 0.33 | 0.33 |
| | 0.33 | 0.35 |
| | 0.36 | 0.36 |
| | 0.35 | 0.34 |
| | 0.38 | 0.38 |
| | 0.36 | 0.36 |
| | 0.34 | 0.34 |

* Tracing 16 of experiment 1, after the administration of 80 per cent of the average fatal dose of digitalis intravenously. r = ventricular or nodal ectopic beats; — = unable to read intervals with precision; p = inverted auricular deflection.

*Ectopic Beats Produced by Struggle After Small Dose; Rate Slower Than That of Sinus Before Struggle.*—Eighty-two minutes after the second dose, a third injection of 10 per cent was made (total was 80 per cent of the average fatal dose in one hundred and two minutes). Three minutes later, struggling produced ventricular ectopic beats. During the subsequent period of two and three-quarter hours the string was watched continuously. It was noted that there was a normal sinus rhythm when the animal was quiet, and that the ventricular ectopic beats appeared temporarily after struggling. This effect of struggling was repeated eighteen times with only one failure during this period.

The conditions attending the production of ectopic beats by struggling after the administration of this dose of digitalis to this animal

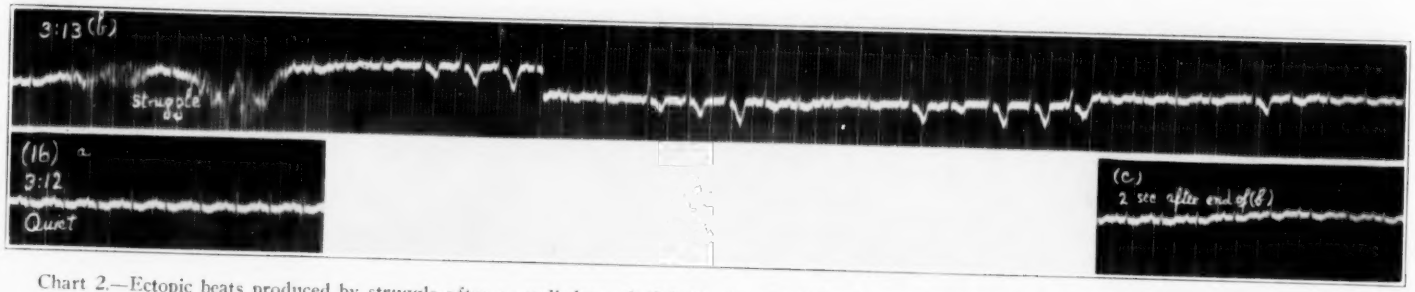


Chart 2.—Ectopic beats produced by struggle after a small dose of digitalis, the rate being slower than that of the sinus before the struggle. Note the effect of the exaggerated sinus arrhythmia.

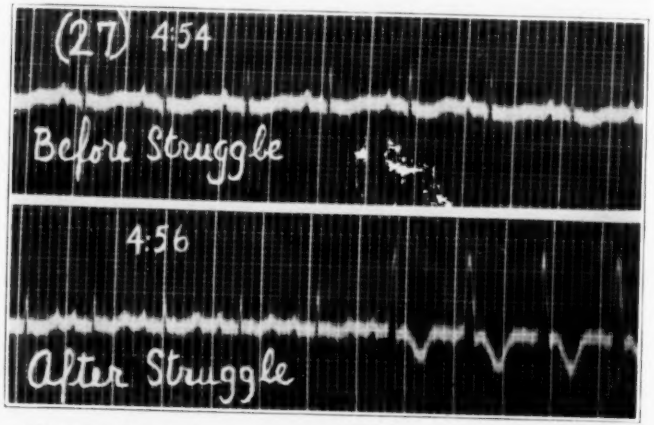


Chart 3.—Ectopic beats produced by struggle after a larger dose of digitalis, the rate being slightly faster than that of the sinus before the struggle.

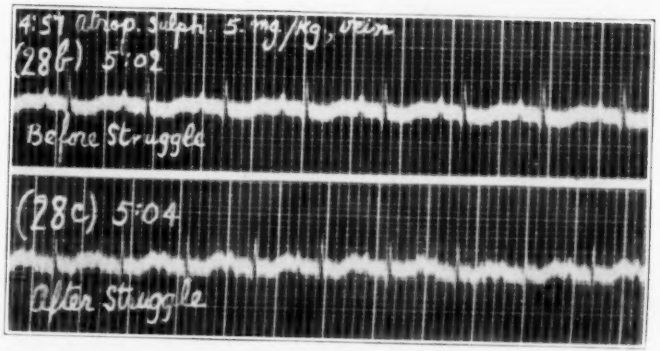


Chart 4.—Struggle fails to produce ectopic beats after paralysis of the vagi.

are illustrated in chart 2 and table 1. We refer to this period as the "vagal phase" of digitalis action (explained in the next section). Immediately before the struggling, a normal sinus rhythm was present with an R-R interval of 0.32 second. During the quiet period after the struggling, several periods of ectopic beats occurred, interrupted by short series of normal beats. The ectopic beats often occurred early in the cycle and their rate was slower than that of the sinus in the control; the r-r interval was 0.36 to 0.39 second. After the struggling a very marked and rapidly changing sinus arrhythmia was present, the P-P interval during the rapid phase being as low as 0.32 second and during the slow phase as high as 0.44 second. The ectopic beats were not present immediately following the struggle, but appeared after an interval of about one second. None of the four series of ectopic beats began during the period of the rapid sinus rate; they began only after the latter had slowed considerably below the resting rate of the control. Thus, while the R-R interval before struggling was 0.32 second, the interval lengthened in each case to 0.39 second or more before ectopic beats appeared. In the early part of the tracing, in which ectopic beats occurred, the P-P intervals varied between 0.32 and 0.44 second, and in the latter part, when ectopic beats were absent, the variations were much smaller, between 0.33 and 0.38 second. As the intensity of the sinus arrhythmia diminished, therefore, the ectopic beats disappeared. The rate of the ectopic beats was most rapid at first and then gradually became slower. Thus the r-r interval of the first series was 0.36, of the second series from 0.36 to 0.37 and of the third series from 0.37 to 0.39 second.

Chart 4.—Struggle fails to produce ectopic beats after paralysis of the vagi.

digitalis, the rate being slightly faster than that of the sinus before the struggle.

We have already noted that the interval between the R wave of the last normal beat and that of the first ectopic beat (the R-r interval) was constant, about 0.39 second in the record of table 1. However, this interval following a given dose of digitalis was not the same after different struggles, as one would expect, since it is obviously impossible to produce any two struggles of exactly the same intensity or duration. Table 2 shows some of the e variations. The records of eight tracings are reproduced, taken from the same animal and after the injection of the same dose of the drug. These tracings are similar to those in chart 1, each having been taken after a period of struggling. Table 2 also shows that ectopic beats occurred only after marked slowing of the sinus rate and that the amount of slowing before the appearance of ectopic beats in the different tracings was not the same. In one instance, the ectopic beats appeared after a P-P interval of 0.38 second, while in another case, they were absent even after a P-P interval of 0.61 second. After a given struggle, however, the amount

of slowing in the sinus rate before ectopic beats occurred showed a certain type of constancy if more than one series of ectopic beats, interrupted by a series of normal beats, was present in the record. Thus in tracing 11 (table 2), each of the two series of ectopic beats began when the sinus rate had slowed to a P-P interval of 0.64 second; in tracing 12, the interval in each case was 0.47 second, and so on. This was, however, not absolutely constant (tracing 15, table 2). Furthermore, while a slowing to a P-P interval of 0.38 second was followed by ectopic beats in tracing 14 *d*, a greater slowing to 0.40 second in tracing 13 was not followed by ectopic beats. As far as

TABLE 2.—*Variations in the Slowing of the Sinus Rate Before the Appearance of Ectopic Beats Following Struggles of Different Intensity and Duration*

| Tracing | Longest P-P Interval of Normal Rhythm, Seconds | P-P Interval Between Last Normal and First Ventricular Ectopic Beat, Seconds | Series of Ectopic Beats in the Tracing |
|---|---|---|---|
| 10 | 0.43 | 0.48 | One |
| 11 | 0.44 | 0.64 | First |
| | 0.61 | 0.64 | Second |
| 12 | 0.38 | 0.40 | First |
| | 0.38 | 0.47 | Second |
| | 0.38 | 0.47 | Third |
| 13 | 0.40 | .... | None |
| 14-c | 0.40 | 0.52 | First |
| 14-d | 0.36 | 0.42 | First |
| | 0.36 | 0.38 | Second |
| | 0.36 | 0.38 | Third |
| 14-e | 0.38 | 0.44 | First |
| | 0.38 | 0.44 | Second |
| 15 | 0.36 | 0.46 | First |
| | 0.36 | 0.40 | Second |
| | 0.36 | 0.41 | Third |
| | 0.36 | 0.52 | Fourth |
| | 0.36 | 0.52 | Fifth |
| | 0.36 | 0.52 | Sixth |
| | 0.36 | 0.52 | Seventh |

one could judge, the weakest struggle preceded tracing 13 and the strongest struggle in this period preceded tracing 14 *d*. It is therefore clear that if the slowing of the sinus rate following a struggle stands in any causal relation to the appearance of ectopic beats in the partially digitalized heart, it is not the only factor responsible for their appearance.

*Ectopic Beats Produced by Struggle After Larger Dose; Rate Slightly Faster Than Sinus Rate Before Struggle.*—In three hours after the last dose of digitalis, struggling no longer called forth ectopic beats. Occasionally a single ectopic beat would appear after a strgugle; there were six struggles in a period of seventeen minutes. We interpreted this result as due to the elimination of the rapidly eliminated fraction of digitalis, since sufficient time had elapsed for this to occur. An additional dose of 10 per cent was then injected, and two minutes later struggling was again effective in producing ectopic beats. The conditions attending the appearance of ectopic beats after this larger dose of digitalis are shown in

chart 3 and table 3. The P-P interval of the period before the struggle was practically the same as that after administration of the 80 per cent dose in table 1, namely, 0.32 second. Again ectopic beats did not appear immediately, but began five seconds after the struggle and after the slowest sinus beat of the phase in which recovery takes place. The first ectopic beat occurred early in the cycle, 0.02 second before the supraventricular beat was due, and at a time when the sinus rate had not decreased below that of the resting level, unlike that following the smaller dose of digitalis (table 1). Whereas the ectopic rhythm produced by struggling following the smaller dose was never faster than an r-r interval of 0.36 second, it was never slower than an r-r interval of 0.32 second after the larger dose of digitalis.

*Struggle Fails to Produce Ectopic Beats After Paralysis of Vagi.*—Fifteen minutes after the administration of the last dose of digitalis, the animal received atropine sulphate, 5 mg. per kilogram injected intravenously, to paralyze the vagi. Struggling seven times during the next forty-four minutes failed to produce ectopic beats. A typical record obtained in this period is found in chart 4. The paralysis of the vagi did not accelerate the sinus rate appreciably; the P-P interval

TABLE 3.—*Effect of a Struggle on the Production of Ectopic Beats After the Larger Dose of Digitalis* *

| Time of Recording | P-P Interval, Seconds | R-R Interval, Seconds |
|---|---|---|
| Immediately before struggle (condition of animal: quiet).. | 0.32-0.34 | 0.33 |
| After struggle ..... | 0.27 | 0.28 |
| | 0.30 | 0.32 |
| | 0.32 | 0.30 (R-r) |
| Five seconds after struggle..... | r | 0.32 (r-r) |

* Tracing 27 of experiment 1, after administration of 90 per cent of the average fatal dose of digitalis intravenously. r = ventricular or nodal ectopic beats.

before the injection of atropine was from 0.32 to 0.34 second, and five minutes after the injection it was from 0.32 to 0.33 second (compare 28 *b* of chart 4 with the tracing made before the struggle in chart 3). In the tracings after the struggle (28 *c* of chart 4) with the vagi paralyzed, no P-P interval was longer than 0.28 second. This result was expected, since the slowing action of the vagi on the sinus had been excluded, and a slowing of the sinus then occurred only when the stimulation of the accelerator by the struggling began to subside.

The part played by the vagi was also tested in other ways. In one experiment in which struggling produced ectopic beats after an intravenous injection of 0.15 mg. of digitoxin per kilogram, electrical stimulation of either vagus in the neck produced an ectopic rhythm. In two other experiments in which the vagi were cut during the stage of the action of digitalis in which ectopic beats were produced by struggling, the latter phenomenon disappeared. The exact interpretation of this result was not possible, because marked respiratory disturbances occurred in these instances, and when the trachea was opened to relieve the respiratory distress, marked acceleration of the heart occurred. For these reasons atropine was used to exclude vagal action in most of the experiments.

*Struggle Again Produces Ectopic Beats After Additional Dose of Drug, Though Vagi Are Paralyzed.*—An additional 10 per cent of the average fatal dose of digitalis was injected twenty minutes after the injection of the atropine, and following a delay of about twenty-four minutes ectopic beats again appeared after struggling. Struggling during this delay failed to produce ectopic beats. The record obtained after paralysis of the vagi and after the administration of the

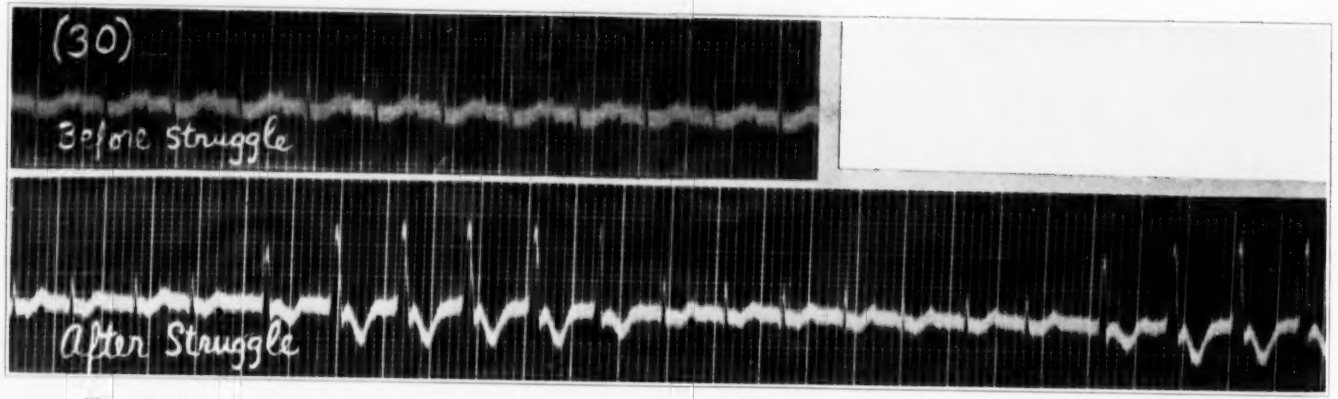


Chart 5.—Ectopic beats produced, despite paralysis of the vagi, by struggle after the injection of an additional dose of digitalis.

100 per cent dose of the drug is shown in chart 5 and table 4. While the sinus rate in the period of rest was not changed by paralysis of the vagi, the injection of an additional dose of digitalis increased the sinus rate of the animal while at rest from a P-P interval of 0.32 to one of from 0.29 to 0.30 second, and the P-R interval was increased from about 0.10 to 0.12 second.

In this record, the ventricular ectopic rhythm appeared following the struggle after the longest pause in the basic rhythm. The absence of definite P-waves after struggling suggests that the basic rhythm after struggling originated in the auriculoventricular node. The other possibility is that the basic rhythm was a sinus rhythm with a long P-R interval, the P-wave being superimposed on the T-wave.

TABLE 4.—*Effect of a Struggle on the Production of Ectopic Beats After Paralysis of the Vagi by Atropine* *

| Time of Recording | P-P Interval, Seconds | R-R Interval, Seconds |
|---|---|---|
| Immediately before struggle (condition of animal: quiet).. | 0.29-0.30 | 0.29-0.30 |
| After struggle | — | 0.25 |
| | — | 0.25 |
| | — | 0.27 |
| | — | 0.22 |
| | — | 0.32 (R-r) |
| Seventeen seconds after struggle | — | 0.28 (r-r) |

* Tracing 30 of experiment 1. — = intervals cannot be read; r = ventricular ectopic beats.

TABLE 5.—*Intervals Between the Cessation of Struggling and the Appearance of Ectopic Beats with the Vagi Intact and After Paralysis of the Vagi by Atropine in Experiment 1*

| Electrocardiogram | Vagi Intact, Seconds | Electrocardiogram | Vagi Paralyzed, Seconds |
|---|---|---|---|
| 16 | 1.0 | 30-b | 15 |
| 18-b | 5.0 | 31-c | 60 |
| 19-b | 2.5 | 32-c | 60 |
| 20-b | 1.0 | 36-b | 25 |
| 21-b | 4.0 | | |
| 21-d | 4.0 | | |
| 26-b | 2.0 | | |
| 27 | 5.0 | | |

In the records made after the injection of the 80 per cent dose, the rate of the ectopic rhythm was slower than that of the sinus rhythm before the struggle; in those after the injection of the 90 per cent dose, the former was nearly equal to the latter, and those after the injection of the 100 per cent dose, the former was faster than the latter.

*Paralysis of the Vagi Delays Appearance of Ectopic Beats.*—In this animal, therefore, with certain doses of digitalis, paralysis of the vagi prevented the production of ectopic beats by struggling. When the dose of digitalis was increased, ectopic beats again occurred, even in the absence of the vagal influence, but there was marked delay between the struggle and their appearance. This is shown in table 5.

Whereas they appeared in from one to five seconds when the vagi were intact, there was a delay of from fifteen to sixty seconds after the vagi were paralyzed.

Since ectopic beats were produced by the larger doses of digitalis forty-four minutes after the administration of atropine, the possibility was considered that their reappearance might have been due to at least partial recovery of the vagi in this period of time, rather than to the additional quantity of digitalis acting in the absence of control of the vagus. That this was not the case, however, was shown by the fact that when the dose of atropine was repeated one hour after the first dose, it was entirely without influence on the phenomenon of the production of ectopic beats by struggling.

## COMMENT

In the course of the work we discovered that when digitalis is injected slowly intravenously (from 5 to 10 per cent of the average fatal dose at consecutive intervals of from five to ten minutes) the occurrence of subauricular ectopic beats can in most cases be divided into two stages in the order of the quantity of the drug required: (1) the stage in which ectopic beats may be produced or abolished by struggling and (2) the stage in which the ectopic beat or rhythm occurs and remains uninfluenced by struggling. This was demonstrated in another way during the period of elimination of the drug. In several experiments the following phenomena were observed: A given dose of digitalis produced ectopic beats only after struggling; the dose was increased with the result that a spontaneous ectopic rhythm (without struggling) appeared; this persisted for varying periods of time (sometimes for days), after which the tracings for the control again showed a normal sinus rhythm with ectopic beats produced by struggling only; the latter, after varying periods of time (for several days in some experiments), was followed by a condition in which ectopic beats were absent in the resting period and could not be produced by struggling. The dosage necessary to produce the first stage varied from about 40 to 75 per cent of the average fatal dose. The percentage of the actual fatal dose for a given animal producing the various phenomena was not considered, because the total quantity was given in several doses. These experiments frequently lasted for many hours; hence, considerable elimination of previous doses took place.

We found, further, that both stages of action may be produced (*a*) in the intact animal, (*b*) after the vagi are severed in the neck or paralyzed by atropine, and (*c*) after double vagotomy in addition to the removal of both inferior cervical and stellate ganglions. An

analysis of the details of the results in relation to the doses of the drug revealed differences in the behavior of this phenomenon which show that while under certain conditions neither the vagi nor the stellate ganglions are essential, they may play an important rôle when they are intact.

The individual experiments yielded results that are in many cases seemingly contradictory owing to the counterplay of several forces. These forces are at times difficult to follow, and it is hard to estimate the rôle played by each because they may all be brought into play at the same time, but most of the observations may be correlated if interpreted in the light of certain generally accepted views relating to the physiology of the heart and the action of digitalis: 1. The injection of digitalis directly increases the rhythmicity of the various cardiac structures capable of initiating impulses, the sinus, the auriculoventricular node, and the ventricle. 2. The center with the highest rhythmicity tends to become the pacemaker. 3. The vagus and sympathetic nerves act on some of these structures to change their rate and by stimulation serve to intensify the direct action of the drug, and the vagi do not alter ventricular rhythmicity directly, while sympathetic stimulation acts directly to increase it (Rothberger and Winterberg).

In experiment 1, while struggling produced ventricular ectopic beats, the appearance of the latter depended to a large extent on changes occurring in the recovery phase after the struggle (chart 2). Struggling depresses the vagi and stimulates the accelerator nerves. The sinus rate is increased as a result of a combination of these two actions in various proportions. The sinus acceleration alone tends to prevent the appearance of ventricular ectopic beats, while the simultaneous action of the accelerator nerves on the ventricle favors their production. For a short period after the struggling, vagal tone frequently increases beyond that of the rest period before the struggle. After the 80 per cent dose of digitalis in this experiment, the ventricular ectopic rhythm produced by struggling was slower than the sinus rate of the animal at rest, hence, the vagal factor in its production. For this reason, and for convenience of discussion we refer to this as the "vagal phase" of the action of digitalis. That this dose of the drug had increased the rhythmicity of the ventricle was seen from the fact that a struggle following a smaller dose failed to call forth ectopic beats, even though a greater amount of slowing of the sinus rate had occurred (chart 1). Thus far, only two factors could be detected; first, digitalis had increased the rhythmicity of the ventricle by a direct action; second, the vagal tone had been markedly increased above normal in the recovery phase after the struggle, thereby making the sinus pacemaker slower than the ventricle and allowing the latter to

obtain temporary control. As the vagus released the sinus during the period of exaggerated sinus arrhythmia, the ectopic rhythm disappeared.

Evidence that struggling also produced a direct change in the ventricle was obtained only after injection of the larger dose of the drug (90 per cent of the average fatal dose). In this case the rate of the ectopic rhythm induced by struggling was the same as, or slightly more rapid than, the sinus rate of the animal at rest (chart 3). Here then, it is apparent that the rhythmicity of the ventricle had increased as the result of the struggle, and in all probability due to stimulation by an accelerator. The effect was not seen immediately after the struggle because of the simultaneous acceleration of the sinus rate (above that of the ventricle). The effect of stimulation by an accelerator on the ventricle lasted longer, however, than that on the sinus, as one would expect, since the sinus recovers after struggling, not only by the disappearance of sympathetic action but by active return of vagal control. The term "accelerator phase" is used by us to indicate the period of action of digitalis in which struggling produces ventricular ectopic beats, the rate of which is the same as, or exceeds that of the sinus before the struggle.

Depending on a number of circumstances, the appearance of ectopic beats after struggling was either prevented, delayed or uninfluenced by paralysis of the vagi. With the smaller doses of the drug, in cases in which depression of the sinus was necessary before the latter became slower than the ventricle, the vagal factor was essential (chart 4). At this stage complete paralysis of the vagi prevented the heart from slowing sufficiently to produce ectopic beats after struggling. When the dose of the drug was increased, the accelerator factor excited by struggling became sufficient to produce ectopic beats even in the absence of vagal control (chart 5), but there was considerable delay in their appearance. This delay is caused by the simultaneous acceleration of the sinus, which takes longer to slow in the absence of the return of vagal tone. It is not possible to compare the actual intervals of time in one animal with those in another because of the marked variations. The rôle of the vagus in the delay is demonstrated, however, by the fact that in any single animal paralysis of the vagi under given conditions may delay the appearance of ectopic beats after struggling (table 5). The delay may conceivably last long enough to permit the recovery of the ventricle and thus prevent the appearance of ectopic beats after a struggle.

When still larger doses of digitalis were given to this animal, struggling produced ectopic beats with little or no delay even in the absence

of vagal control, because the rhythmicity of the ventricle in the period of rest was now so marked that the addition of the accelerator factor by struggling rendered the rate of the ventricle equal to or more rapid than that of the sinus. Under these circumstances, paralysis of the vagi proved to be without visible influence on the production of ectopic beats by struggling. This shows that the part played by the vagus and the sympathetic nerves is not a fixed one, and that with change in the conditions of the experiment very different results may be obtained; the rôle of these nerves may change from one in which they are essential to one in which they seem to play no part.

In this experiment, therefore, two distinct phases in the action of digitalis may be recognized: (1) the "vagal phase," in which an essential factor in the production of ectopic beats by struggling is the increased vagal tone after the struggle, and in which paralysis of the vagi may prevent the appearance of ectopic beats after a struggle; (2) the "accelerator phase," in which struggling produces ectopic beats even after paralysis of the vagi, though the severity of the struggle, the interval before the appearance of the ectopic beats or their duration may be modified. The former phase occurs after the relatively smaller doses of the drug, the latter after the larger ones.

Since the tone of the vagus varies greatly in different animals and may be absent in some, it is to be expected that in the animal in which the tone is low during the period of rest and in which little increase occurs after struggling, the vagal phase in the action of digitalis will be absent. An example of this was found in experiment 3. While 70 per cent of the average fatal dose of digitalis slowed the sinus rate from about 200 to about 84 beats per minute in experiment 1, the degree of slowing at all times in experiment 3 was negligible, from a rate of 200 to one of 190 beats per minute, and throughout the experiment the rate was generally above 200 beats per minute. Ectopic beats appeared later in the period of poisoning, only after 95 per cent of the average fatal dose had been injected in a period of sixty-nine minutes. At no time was the ectopic rhythm (induced by struggling) preceded by perceptible slowing of the sinus and the rate of the former was practically the same as, or faster than, that of the latter. In this animal the paralysis of the vagi by atropine was without influence on the production of ectopic beats by struggling.

Experiments 1 and 3 illustrate two extremes, namely, one in which the vagal phase is marked and one in which the vagal phase is absent. In the first, marked increase of vagal tone occurred almost uniformly after struggling, with the result that struggling in this phase of the action of digitalis failed to call forth ectopic beats only once out of eighteen trials in a period of two and three-quarter hours. In the

second, there was practically no increase of vagal tone; hence the vagal phase was entirely absent. In another experiment the increase of the vagal tone after struggling was extremely irregular (experiment 2) with the result that struggling frequently failed to produce ectopic beats in the vagal phase of the action of digitalis.

The vagal phase made itself evident in another way in experiment 4. Seventy per cent of the average fatal dose of digitalis caused marked slowing of the sinus rate in experiment 1, but no ectopic beats occurred. In experiment 4, 50 per cent of the average fatal dose caused less marked slowing of the sinus rate but at the same time so increased the rhythmicity of the ventricle that a ventricular ectopic rhythm appeared without any struggling. The sinus rate diminished from a P-P interval of from 0.30 to 0.34 second to one of 0.40 second and an ectopic rhythm appeared with an r-r interval of 0.38 second. Under these conditions, struggling by inhibiting the vagus and accelerating the sinus abolished the ectopic rhythm. The vagus remained in a state of partial inhibition during a considerable period of rest as seen from a rather rapid sinus rate (P-P interval 0.28 second). Ectopic beats were then produced during the period of increased vagal tone after a struggle (r-r interval 0.36 second). The importance of the vagal action was again seen when a spontaneous ectopic rhythm (r-r interval from 0.36 to 0.38 second) was reinduced by an additional dose of digitalis while the animal was quiet. This time vagal influence was removed, not by struggling, but by atropine. Atropine sulphate, 10 mg. per kilogram, was injected intravenously and within one-half minute, a normal sinus rhythm was established with a P-P interval of from 0.28 to 0.30 second. During a period of eighteen minutes following the injection of atropine the animal was made to struggle seven times and no ectopic beats were produced, i. e., the addition of the accelerator factor by struggling in the absence of the vagal control was insufficient to produce an ectopic rhythm. When the dose of digitalis was further increased, struggling again produced ectopic beats, but with a rate much higher than in the early part of the experiment, the r-r intervals being from 0.24 to 0.26 second. In this experiment, therefore, struggling both abolished the spontaneous ectopic rhythm and induced an ectopic rhythm when it was absent during the control period.

Thus far we have seen that in a given animal the rate of the ectopic rhythm following a struggle was either the same, slower, or faster than the sinus rate when the animal was at rest after a given dose of digitalis. In experiment 15 a, two phases of action were obtained after the same dose of the drug. Electrocardiogram 11 (chart 6) was taken after an intravenous injection of 0.15 mg. of digitoxin-Merck per

kilogram. The tracing was taken continuously before, during and after the struggle, and illustrative sections 1 to 7 are reproduced. In the control period when the animal was at rest there was a marked sinus arrhythmia, the P-P interval varying from 0.30 to 0.37 second (section 1). This was abolished during the struggle, and immediately afterward the P-P interval was 0.24 second (section 2). The first ectopic beats appeared about thirty seconds after the struggling (sections 3 and 4), and their rate was faster than that of the sinus rate of the control (section 1), namely, r-r intervals of 0.28 and 0.30 second, respectively. During the next thirty seconds eleven short periods

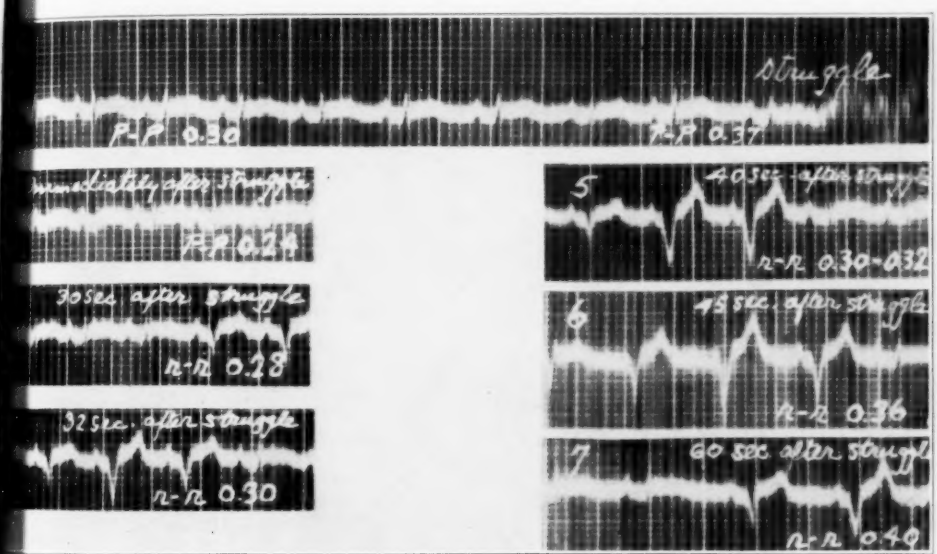


Chart 6.—Electrocardiogram illustrating the occurrence of both the accelerator and vagal phases of the action of digitalis after a single struggle.

of ectopic beats occurred, interrupted by periods of normal beats. The rate of the ectopic beats in the successive periods became progressively slower until the last period, one minute after the struggle, when the ectopic rhythm was slower than the sinus rate of the control animal at rest, namely, an r-r interval of 0.40 second (tracing 7). The sinus rate was now also slower than at any time during the control period before the struggle, the P-P interval being 0.42 second.

In this case the rhythmicity of the ventricle already increased by the direct action of the drug was further increased by the accelerator factor as the result of struggling to such an extent that an ectopic

rhythm appeared with a rate that was faster than that of the resting sinus. As the accelerator factor subsided in the succeeding period of rest, the rate of the ectopic beats diminished. When the ectopic beats became slower than the rate of the resting sinus, they continued to occur only because of the simultaneous increase in the intensity of the vagal action on the sinus. In this experiment the first groups of ectopic beats exhibited the accelerator phase of digitalis action, the later groups, the vagal phase.

### ACTION OF DIGITALIS IN THE PARTIALLY DENERVATED HEART

The following are brief summaries of the three experiments in which the hearts were denervated:

EXPERIMENT 10.—*Heart Denervated; Difficult to Produce Ectopic Beats by Struggle.*—In this experiment the inferior cervical and the stellate ganglions were both removed during ether anesthesia, and after the animal recovered from the ether in a period of over two hours, the injection of ouabain was started. The heart rate in the absence of sympathetic innervation was slow when compared with that of the average unanesthetized cat tied down on the table, namely, an R-R interval of from 0.44 to 0.46 second. The P-waves varied from the positive through the intermediary stages to the negative sign, indicating in all probability a shifting of the pacemaker from the sinus to the auriculoventricular node. This shifting continued to occur during the administration of ouabain. After the vagi were severed there was severe struggling, and the heart rate increased to a P-P interval of from 0.37 to 0.38 second. The sinus then slowed to a P-P interval of from 0.41 to 0.42 second; thereafter only minor variations in the sinus rate were present during the resting period and struggling produced only slight acceleration (3 or 4 beats per minute).

Usually, the cutting of both vagi in the necks in cats results in respiratory disturbances due largely to closure of the larynx, necessitating tracheotomy. In this animal breathing became entirely normal after the initial struggle. Forty-seven minutes later the animal struggled violently and this was attended by what seemed to be respiratory difficulty; hence a tracheal cannula was inserted. The struggle may have induced a spasm of the laryngeal muscles.

After injection of 62 per cent of the average fatal dose of ouabain, a violent struggle called forth a ventricular ectopic rhythm in which the ectopic beats were coupled and the rate (r-r intervals of 0.32 and 0.42 second) was more rapid than the previous sinus rate by about 12 beats per minute. No rate for the animal at rest was obtained after the administration of this dose. The string was watched continuously, and ectopic beats were seen to appear just after spontaneous struggle. After the ectopic rhythm disappeared, further struggling failed to recall it.

The dose of ouabain was increased to 73 per cent, after which the resting sinus rate showed a P-P interval of from 0.39 to 0.40 second. Immediately after the animal struggled, the rate accelerated to a P-P interval of from 0.36 to 0.38 second (an increase of about 10 beats per minute), and every other beat was a ventricular premature contraction. When this rhythm disappeared, repeated struggling again failed to recall it. After the larger doses of ouabain, a slight struggle produced a ventricular ectopic rhythm the rate of which was more rapid, and the focus of which was frequently changed by struggling. This persisted

until the appearance of ventricular fibrillation. The rate of the ectopic rhythm was never faster than an r-r interval of 0.32 second.

EXPERIMENT 11.—*Struggling Fails to Produce Ectopic Rhythm.*—The heart was denervated in a manner similar to that in experiment 10. Double vagotomy performed after the excision of the inferior cervical and stellate ganglions was again without influence on respiration after a temporary disturbance. The heart rate of the animal while at rest was quite rapid (P-P interval from 0.30 to 0.31 second), and struggling resulted in practically no acceleration of the sinus (P-P interval from 0.29 to 0.32 second). It was found impossible to produce ectopic beats by struggling with any dose of ouabain. An ectopic rhythm appeared only after the fatal dose had been injected and persisted until death. This animal was more susceptible than the average, requiring only about 71 per cent of the average fatal dose to cause death. The heart continued to beat for about one minute after cessation of respiration, a condition that is not often seen in normal animals after a fatal dose of ouabain.

It is not possible to know what bearing the denervation had on the greater susceptibility and the cessation of respiration before the heart beat. Both phenomena are sometimes seen in normal cats, and both were absent in the other two animals with denervated hearts.

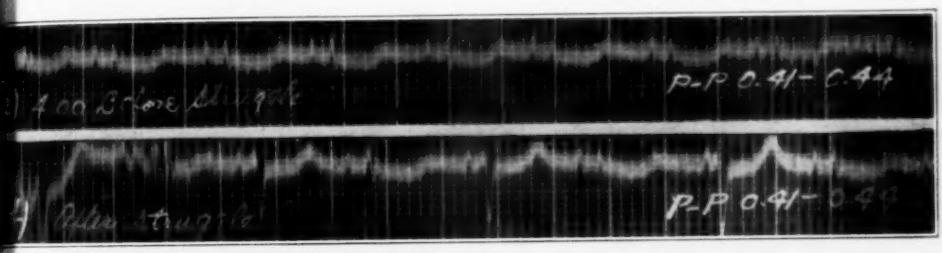


Chart 7.—Ectopic beats produced by struggle in the denervated heart after the injection of ouabain. Note the absence of changes in the sinus rate.

EXPERIMENT 12.—*Results Similar to Those of Experiment 3.*—The same denervation was carried out. It was unnecessary to perform tracheotomy because after a temporary disturbance respiration was quite normal throughout. As in experiment 10, a spontaneous shifting of the pacemaker from the sinus to the auriculoventricular node and back to the sinus was seen in several tracings. The fatal dose of ouabain was practically the same as that for the normal cat, namely, 0.095 mg. per kilogram. Struggling produced no acceleration of the sinus rate until 45 per cent of the average fatal dose had been injected, when the sinus rate increased from a P-P interval of 0.42 to one of 0.36 second after a struggle. The highest sinus rate was one with a P-P interval of 0.33 second while the animal was quiet following 53 per cent of the fatal dose. Struggling after the latter dose produced no acceleration of the sinus, in fact, there was a decrease in rate by 3 beats per minute. Tracings 11 *a* and 11 *b* of chart 7 serve to illustrate the conditions under which ectopic beats appeared. These were called forth by a struggle after 61 per cent of the fatal dose of ouabain. There was no acceleration of the sinus rate after the struggle, and no slowing of the sinus preceded the appearance of the ectopic beats. The cat reacted in a manner similar to that of the animal in experiment 3; when the dose was increased, a slight struggle called forth a ventricular ectopic rhythm, the rate of which, however, was slower than in the latter experiment, never exceeding an r-r interval of 0.36 second.

We have been referring to the stage in the action of digitalis in which struggling produces or abolishes subauricular ectopic beats as divided in a general way into the vagal phase and accelerator phase. This has been so expressed to signify that at a relatively early stage when the rhythmicity of the ventricle has not been greatly increased, the rate of the ventricular ectopic rhythm produced by struggling is usually slower than the rate of the sinus when the animal is at rest, hence the increased vagal tone is essential to its appearance, and that at a relatively later stage of action, the rate of the ventricular ectopic rhythm induced by struggling is equal to, or faster than, the resting rate of the sinus and action of the vagus is of little or no importance. The latter we have referred to as mediated through the sympathetic nerves, hence the accelerator phase.

In the matter of the part played by the vagus in the two phases of the action of digitalis there are some exceptions. Occasionally, slowing of the sinus rate below that of the control occurs after the vagi have been paralyzed. It is conceivable that the reaction of the vagal phase might occasionally be given by the denervated heart because, as Cannon and his associates [8] have shown, the sinus rate in the latter is sometimes slowed after a struggle. Similarly, paralysis of the vagi may sometimes prevent the appearance of ectopic beats even in the accelerator phase, owing to the relative excessive acceleration of the sinus rate by the struggling after the exclusion of vagal control over the sinus as seen in experiment 1 (chart 4).

Usually, however, paralysis of the vagi abolishes the phenomenon occurring in the vagal phase of the action of digitalis. It is now necessary to see what direct evidence may be adduced for the responsibility of the sympathetic nerves in the production of ectopic beats by struggling in the accelerator phase of the action of digitalis. If the sympathetic nerves are wholly responsible for the latter action, complete denervation of the heart should render it impossible to produce ventricular ectopic beats by struggling. If other factors are also involved (humoral or dynamic), complete denervation should simply modify the phenomenon. The results were quite variable in the experiments after double vagotomy and excision of both the inferior cervical and the stellate ganglions; in one, it was found impossible to induce ectopic beats by struggling; in another, the phenomenon was modified, losing the sensitiveness of a nervous reflex so that a violent struggle was necessary to produce ectopic beats, and repeated struggling failed to recall them; in the third case, the reaction was quite similar to that of the accelerator phase in a normal animal.

8. Cannon, W. B.; Lewis, J. T., and Britton, S. W.: Am. J. Physiol. **77**:326, 1926.

We refer to the production of ectopic beats by struggling after double vagotomy and excision of both the inferior cervical and the stellate ganglions as the residual phase of the action of digitalis. That accelerator stimulation plays an important rôle in the accelerator phase is extremely probable, as seen from the observations of Rothberger and Winterberg [6] by direct electrical stimulation of the stellate ganglions in digitalized dogs, as well as from the observations in our own experiments. But we have no data on which to base a statement as to the part played by other factors (humoral and dynamic) in this phase, and the part played by the accelerator nerves in the residual phase. This is due in the first instance to the difficulty of knowing when the heart is completely denervated. Cannon and his collaborators [8] stated that the operation of double vagotomy and the removal of both stellate ganglions are equivalent in effect to complete denervation of the heart in acute experiments. They found that acceleration of the heart produced by struggilng under these conditions was due to humoral factors (a secretion from the suprarenal glands and the liver). When the latter were excluded by excision of the gland or section of its nerve supply, struggling produced little or no acceleration of the heart rate. In survival experiments, after the foregoing operations, acceleration due to struggling again occurred which, it was found, resulted from the appearance of activity in sympathetic fibers to the heart from the thoracic chain frequently below the fourth segment. When the thoracic sympathetic nerves were also removed, acceleration from struggling was practically entirely abolished until regeneration of the paths (in thirty days or longer). These so-called completely denervated hearts still showed acceleration of from 4 to 14 beats (humoral factors have also been excluded) per minute when the animal struggled. Since our denervation experiments were acute, the view of Cannon and his co-workers would make it necessary to assume that in effect the heart was completely isolated from connection with the central nervous system, and further to assume that the residual phase is due to a humoral or dynamic rather than to a nervous factor. An objection to this assumption, however, arises from the possibility that the presence of a few sympathetic fibers might be insufficient to influence the sinus node, yet quite sufficient to affect the sensitized ventricle. Cannon and his collaborators [8] used heart rate (presumably sinus rate) as the only criterion of cardiac innervation, and there is no evidence against the possibility that the sympathetic nerves might still be acting directly on the ventricle when there is no indication of a connection of the sinus with the central nervous system. At present, therefore, it is not possible to state whether the residual phase is due to humoral or

dynamic factors or to the activity of sympathetic fibers to the ventricle which give no evidence of their presence by the behavior of the sinus node. Further light will be thrown on this subject by more complete cardiac denervation and the exclusion of the glands of internal secretion.[5]

## SUMMARY AND CONCLUSIONS

1. If an animal struggles while under the influence of digitalis, subauricular ectopic beats (ventricular or nodal) may be produced, abolished or left unaffected. The conditions that determine these different effects of struggling and the mechanism involved formed the subject of the present study.

2. Subauricular ectopic beats after the injection of digitalis occur in two stages, depending on the dose: (1) the stage in which they are called forth or abolished by struggling; and (2) the stage in which they appear spontaneously and remain uninfluenced by struggling (the focus may be changed by struggling in this stage).

3. The production or abolition of ectopic beats by the struggling of the digitalized animal does not depend on any single factor, but appears to be governed by the change in the relative rhythmicity of the sinus and the ventricle (or auriculoventricular node) resulting from the struggle.

4. The tendency to increased slowing of the sinus rate after struggling (below that of the sinus rate of the resting animal before the struggle) favors the production of ectopic beats. The slowing of the sinus rate is particularly necessary after the smaller doses of the drug when the rhythmicity of the lower centers is not very marked.

5. We have used the term "vagal phase" of digitalis action to designate that phase in which the rate of the ectopic beats produced by struggling is slower than the sinus rate before the struggle. The vagal phase occurs in animals with a very active vagal tone and after the relatively smaller doses of the drug. It is absent in animals with a low vagal tone. Paralysis of the vagi usually prevents struggling from producing ectopic beats in this phase of digitalis action.

6. In animals with a very active vagal tone, a relatively small dose of digitalis may call forth an ectopic rhythm which may then be abolished by struggling, owing to inhibition of the vagal influence on the sinus.

7. We have used the term "accelerator phase" of the action of digitalis to designate the phase in which the rate of the ectopic beats produced by struggling is equal to, or faster than, the sinus rate before

the struggle. It occurs after the relatively larger doses of the drug. Paralysis of the vagi in the accelerator phase usually does not prevent the production of ectopic beats by struggling.

8. When the vagi and accelerator nerves are intact, they both play important though variable rôles in the production and abolition of ectopic beats by the struggling animal. Under certain conditions, however, struggling may produce ectopic beats in the digitalized animal after paralysis of the vagi and also after the removal of both the inferior cervical and the stellate ganglions in addition. The possible factors involved in this residual phase of digitalis action are discussed.

# THE RELATION BETWEEN THE SO-CALLED RENAL LESIONS OF PLASMAPHERESIS IN DOGS AND CONTRACTED KIDNEYS IN MAN*

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## HISTORICAL REVIEW

From time to time reports have appeared in medical scientific literature describing experimental renal lesions supposed to resemble the characteristic morphologic processes of Bright's disease as it occurs in man. The variety of ways in which renal lesions have been produced is all the more remarkable since few of the methods employed in the experimental studies are in any manner effective in, or relevant to, the natural course of chronic diseases of the kidneys seen in man. A review of these procedures was published in 1924.[1]

It was soon recognized by competent pathologists that there were at least two significant errors in the interpretation of the experimental nephropathies. In the first place, "spontaneous" disease of the kidneys in the particular animals employed was either entirely overlooked or inadequate allowance was made for them. In the second place, and this, unfortunately, seems to be a reflection on the investigator's knowledge of the details of the pathologic process of nephritis in human beings, the experimental renal lesions did not really resemble or duplicate, to any reasonable extent, the anatomic picture of chronic nephritis in human beings. In other words, "spontaneous" nephropathy occurs commonly in all sorts of animals used in the laboratory, but it is easily distinguished by a capable pathologist from the chronic nephritis of man. The frequently reported production of experimental chronic nephritis seems to simmer down to the periodic rediscovery, and possibly reproduction, of the "spontaneous" nephropathies. To this day no one has yet repeatedly produced a diffuse chronic nephritis—glomerulonephritis, more specifically—in any species of laboratory animal, and the picture of contracted kidneys such as occurs in chronic arteriolar sclerosis

* Submitted for publication, Nov. 8, 1930.

* From the Lasker Foundation for Medical Research and the Department of Medicine of the University of Chicago.

1. Leiter, L.: Experimental Chronic Glomerulonephritis, Arch. Int. Med. **33**:611 (May) 1924.

has not as yet been obtained. Such an accomplishment, however, would seem to be of the utmost importance in the understanding of Bright's disease.

The interesting feature of "spontaneous" nephropathies in various domestic animals is the relative uniformity of the pathologic process.

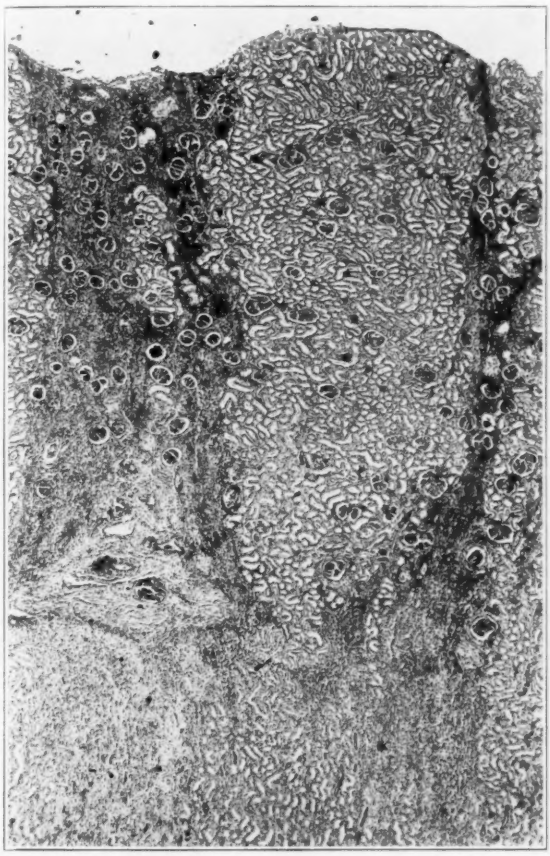

Fig. 1 (dog 10).—Focal scars, causing a granular, pitted surface. Atrophic tubules, mononuclear cell infiltration and periglomerular fibrosis in these scars complete the picture of "spontaneous" interstitial nephritis. Reduced from a magnification of × 30.

Whether one is dealing with the kidneys of the rabbit, the dog, the cat or the calf seems to make little difference. In all of these one is apt to find typical perivascular or interstitial foci of mononuclear cells,

with varying numbers of small lymphoid cells, eosinophils and other polymorphonuclears, distributed in varying degrees throughout the renal cortex. The foci are usually more marked near the boundary zone, but they often extend in linear fashion all the way up to the surface and some distance down into the medulla (figs. 1, 2, 3 and 12). In such areas, if they are at all extensive, varying degrees of atrophy of compressed renal tubules may be seen. In advanced stages fibroblasts appear, and the originally heavily infiltrated regions become scars,

Fig. 2 (dog 14).—Mononuclear cell infiltration and atrophy of the corresponding tubules, in the boundary zone. This represents an early stage in "spontaneous" interstitial nephritis. Reduced from a magnification of × 120.

linear or wedge-shaped, radiating through the entire kidney and containing the débris of atrophied tubules and glomeruli with fairly normal tufts and concentric masses of connective tissue about the parietal layer of Bowman's capsules (figs. 1, 4, 6, 9 and 11). Some of the tufts may be shrunken; occasionally they are adherent to their capsule, and they rarely undergo hyalinization. The fibrosis is usually most marked in the inner part of the cortex and the upper part of the medulla. (figs. 1, 5, 8 and 10). When this focal scarring is extreme, there may be a superficial resemblance to the contracted granular kidney

of chronic nephritis in man. However, there is always considerable normal renal parenchyma intervening between the scarred regions. Renal insufficiency is, therefore, only a remote possibility even in the contracted kidneys. The significant feature of the whole process is its predominantly interstitial character. The glomeruli and tubules are only involved secondarily, the blood vessels hardly at all. This, of course, is radically different from the sequence of events in chronic nephritis in human beings. Excellent descriptions of the renal lesions

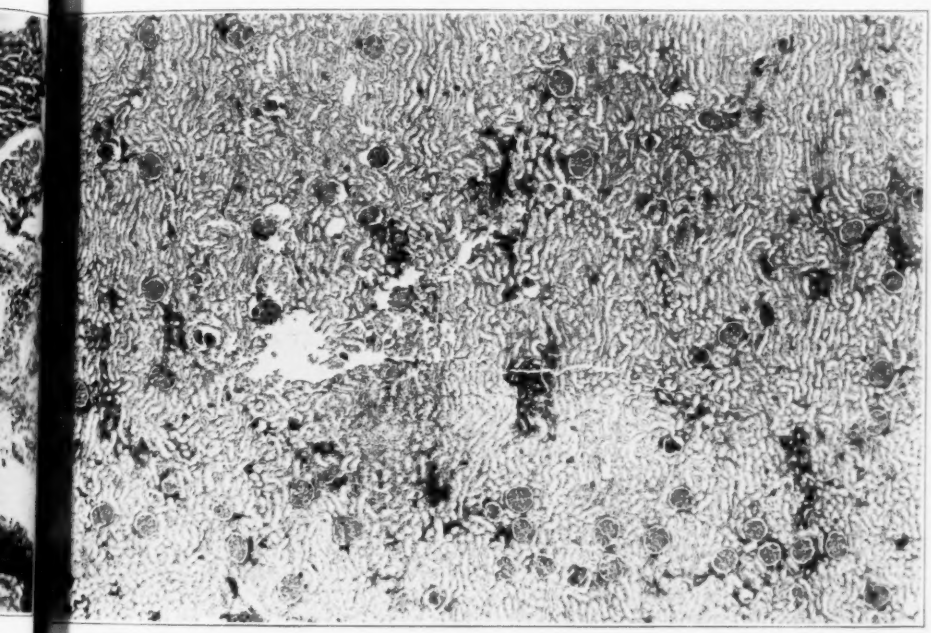

Fig. 3 (dog 34).—Multiple foci of perivascular and periglomerular mononuclear cell infiltration in various levels of the renal cortex. Reduced from a magnification of × 33.

in "spontaneous" nephritis have been published by Ophuls,[2] Dayton,[3] LeCount and Jackson,[4] MacNider,[5] Bloomfield,[6] Bell and Hartzell,[7]

2. Ophuls, W.: J. M. Research **18**:497, 1908.
3. Dayton, H.: J. M. Research **31**:177, 1914.
4. LeCount, E. R., and Jackson, L.: J. Infect. Dis. **15**:389, 1914.
5. MacNider, W. de B.: J. M. Research **34**:177, 1916.
6. Bloomfield, A. L.: Bull. Johns Hopkins Hosp. **30**:121, 1919.
7. Bell, E. T., and Hartzell, T. B.: J. Infect. Dis. **24**:618 and 628, 1919.

Henschen,[8] Roth and Bloss,[9] Bell, Clawson and Hartzell,[10] Smith,[11] Berger [12] and McFadyean.[13] Any one who attempts to interpret experimental chronic nephritis in laboratory animals might spare himself possible disillusionment and avoid drawing conclusions misleading to other workers in this field if he would carefully read these articles.

Fig. 4 (dog 33).—Typical linear area of mononuclear infiltration and beginning fibrosis. Reduced from a magnification of × 95.

8. Henschen, F.: Acta med. Scandinav. **53**:774, 1921.
9. Roth, W., and Bloss, K.: Virchows Arch. f. path. Anat. **238**:325, 1922.
10. Bell, E. T.; Clawson, B. J., and Hartzell, T. B.: Am. J. Path. **1**:247, 1925.
11. Smith, T.: J. Exper. Med. **41**:413, 1925.
12. Berger, H.: Berl. tierärztl. Wchnschr. **44**:613, 1928.
13. McFadyean, J.: J. Comp. Path. & Therap. **42**:58, 141 and 231, 1929.

The present publication has been stimulated by the recent papers of Barker and Kirk [14] and Barker [15] and the editorial comment [16] connected with them. In view of the widespread interest in this subject, a detailed presentation of my own extensive work seems justified. In the course of several years of experience with plasmapheresis carried out on dogs, during which a nephrotic edema with a low protein content of the edema fluid was produced for the first time in dogs,[17] a variety of renal

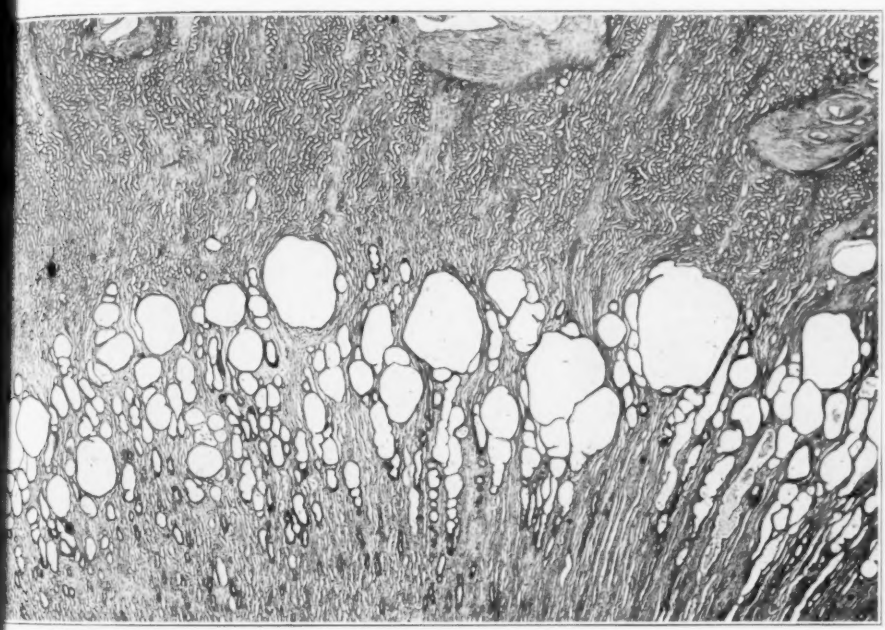

Fig. 5 (dog 41).—Extreme dilatation of collecting tubules in the medulla with marked interstitial fibrosis throughout the boundary zone and the lower part of the medulla. Reduced from a magnification of × 17.

lesions was encountered, most of which could be readily explained on obvious grounds and the rest of which were attributed to "spontaneous"

14. Barker, M. H., and Kirk, E. J.: Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, Arch. Int. Med. **45**:319 (March) 1930.

15. Barker, M. H.: Proc. Soc. Exper. Biol. & Med. **27**:608, 1930.

16. Editorial, The Renal Lesions of Nephrosis, J. A. M. A. **94**:2066 (June 28) 1930.

17. Leiter, L.: Proc. Soc. Exper. Biol. & Med. **26**:173, 1928; **27**:1002, 1930; Experimental Nephrotic Edema, Arch. Int. Med. **48**:1 (July) 1931.

nephropathy, with which a considerable familiarity had been acquired as a result of previous experience and a knowledge of the literature on this subject. It was, therefore, surprising to me that no mention of the possibility of "spontaneous" lesions was found in any of the published material previously mentioned. When the word "spontaneous" is used,

Fig. 6 (dog 41).—Wedge-shaped scar in the cortex causing depression on the surface of the kidney. The usual features of "spontaneous" nephritis are clearly evident. Reduced from a magnification of × 90.

it signifies the naturally occurring nephropathy of the characteristic type that develops independently of the experimental procedure, or renal lesions that are indistinguishable from the natural variety and that appear during the course of, and possibly in some way resulting from, the experimental technic.

It may be stated at once that the various stages of renal lesions described by Barker and Kirk [14] and Barker [15] fit in perfectly with the previously reported forms of "spontaneous" nephropathy in dogs. Cloudy swelling and hyaline droplet degeneration of the tubular epithelium are so common in toxic and infectious processes in the dog that they are of no significance. Fatty changes are to be interpreted in the light of Henschen's vast experience. This author [8] stated that "the kidneys of dogs generally show a physiological fatty degeneration of

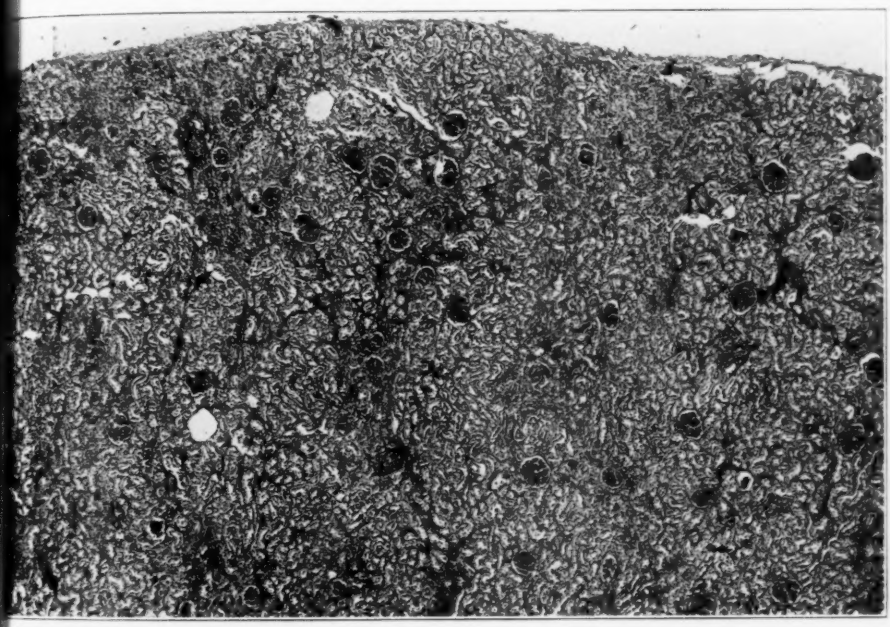

Fig. 7 (dog 85).—Numerous areas of cortical fibrosis, tending to become confluent, without definite granulation of the surface of the kidney. This is an advanced form of chronic interstitial nephritis. Reduced from a magnification of × 35.

the medullary tubules." The evidence consists of autopsies on 220 dogs. MacNider [5] had previously come to an essentially similar conclusion. My own observations in a much smaller series led to the same interpretation. Barker and Kirk presented no satisfactory controls. In regard to their so-called secondarily contracted kidneys, representing, supposedly, the most extensive damage wrought by hypoproteinemia of long duration, Henschen [8] must again be quoted: "Most of these renal atrophies, so usual in dogs, are due to acute interstitial, nonpurulent

nephritis." In other words, dogs have a truly interstitial chronic nephritis. This is readily understood if one accepts Henschen's [8] dictum that "acute interstitial lymphocytic nephritis is the most usual type of acute nephritis" in dogs, resembling the acute interstitial scarlatinal nephritis in man. The "lymphocytes" are eventually replaced by fibroblasts, and focal scars are formed in which the remains of atrophic tubules and shrunken glomeruli may be discerned. Bell, Clawson and Hartzell [10] have more recently come to the same general conclusion concerning renal atrophy or contracted kidney in laboratory animals; they wrote

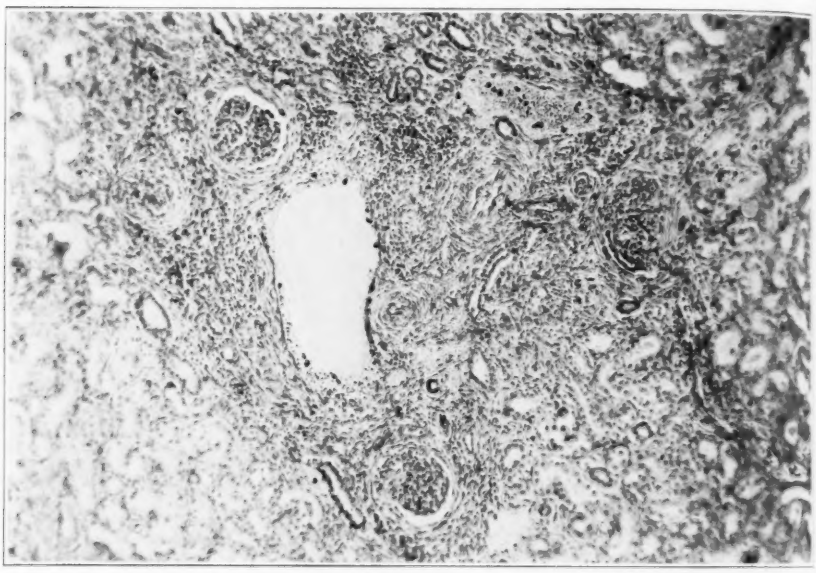

Fig. 8 (dog 85).—Four glomeruli in the inner part of the cortex, to show the concentric fibrosis about Bowman's capsule. The corresponding tubules are atrophic. The arterioles are unaffected. These lesions are probably "spontaneous." Reduced from a magnification of × 110.

that exudative interstitial nephritis caused "the only known form of contracted kidney." Their experience extended over many years. In a comprehensive review of the pathology of nephritis in animals, McFadyean [13] has emphasized the frequent occurrence of "chronic interstitial nephritis," or renal fibrosis, in dogs. He gave excellently detailed descriptions of five instances and made the significant remark that "changes similar in nature and extent are not usually present in either of the forms of contracted kidney in man." The author's photomicrographs strongly support this opinion.

EXPERIMENTAL WORK

Since Barker and Kirk [14] have attributed the renal lesions of their dogs more or less directly to the hypoproteinemia, it would seem profitable to compare the type or stage of renal lesion in my dogs with the duration of the experiment. Approximately 100 dogs were used in this work and about 40 of them were bled sufficiently to reduce the plasma proteins to the level of edema. The accompanying table gives a summary of the essential data, and the photomicrographs illustrate the renal lesions observed. It is obvious that no particular relationship exists between the duration of hypoproteinemia and the degree of renal

*Renal Lesions in Dogs with Hypoproteinemia*

| Dog | Days of Plasmapheresis | Days of Experimental Life | Renal Lesions at Autopsy |
|---|---|---|---|
| 72 | 3 | 3 | Occasional area of mononuclear infiltration |
| 85 | 3 | 4 | Marked fibrosis of the cortex with tubular atrophy; acute focal hemorrhagic nephritis |
| 14 | 5 | 5 | Mononuclear infiltrates; infarct |
| 32 | 5 | 5 | Mononuclear infiltrates; infarcts |
| 15 | 6 | 6 | Perivascular mononuclear infiltrates |
| 33 | 7 | 8 | Slight mononuclear infiltration. |
| 92 | 8 | 14 | Occasional linear cortical scar |
| 10 | 9 | 10 | Focal wedge-shaped areas of granulation tissue in the cortex |
| 11 | 9 | 10 | None found |
| 41 | 11 | 21 | Wedge-shaped cortical scarring; marked fibrosis and cystic dilatation of tubules in medulla |
| 73 | 12 | 20 | Occasional focal mononuclear infiltration or scarring; infarct and abscesses |
| 70 | 15 | 18 | Organizing small infarcts |
| 71 | 15 | 28 | Much perivascular mononuclear infiltration; infarcts and abscesses |
| 17 | 18 | 31 | None found |
| 89 | 18 | 34 | Linear areas of mononuclear infiltration; organizing infarcts |
| 34 | 24 | 36 | Marked mononuclear infiltration; infarcts |
| 69 | 24 | 31 | Medullary abscesses |
| 35 | 29 | 47 | Infarcts and abscesses |
| 90 | 37 | 98 | Organized infarcts |
| 86 | 60 | 139 | Moderate mononuclear infiltration; infarcts in process of organization; no other fibrosis |

damage, if one considers fibrosis or scarring as the most advanced stage. The most extreme renal lesions were found in dog 85 (figs. 7 to 9). In this dog, the kidneys showed little gross scarring or puckering, but there was microscopic evidence of a marked interstitial fibrosis, tubular atrophy and periglomerular fibrosis. This striking nephropathy was present in a dog that had had only three days of plasmapheresis, was then discarded and happened to die of distemper thirty-two days later. Incidentally, an acute focal hemorrhagic nephritis, probably related to the later distemper, was superimposed on the old process. The advanced renal lesions found in dog 41 (figs. 5 and 6) can hardly be correlated with the brief period of plasmapheresis, and they are most likely "spontaneous" in origin.

It occurred to me that the repeated injection of erythrocytes suspended in a saline solution might be partly responsible for the so-called

renal lesions of plasmapheresis. The erythrocytes might clump together enough to embolize small renal arterioles and thus produce minute infarcts with secondary mononuclear infiltration and ultimate fibrosis. Barker and Kirk used aseptic technic throughout, so that experimental infection seemed to be ruled out as a factor in the interstitial nephritis of their dogs. On the other hand, I [18] had not employed aseptic technic and I found the same type of renal lesions, in addition to ordinary infarcts and abscesses that could be attributed to emboli from cardiac

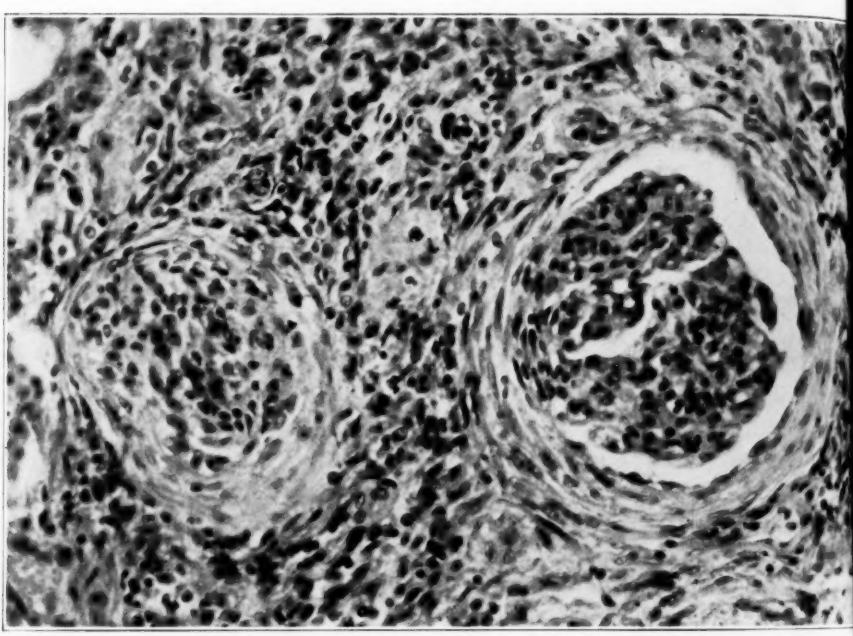

Fig. 9 (dog 85).—Details of the two glomeruli in the upper right hand corner of figure 8. The shrinking of the tufts is secondary to the periglomerular fibrosis. Note the cellular infiltration and the degenerating tubules. Reduced from a magnification of × 400.

vegetations of traumatic origin. In view of all this, a control series of dogs was given daily intravenous injections of from 200 to 400 cc. of a suspension of donors' erythrocytes in a saline solution. Nothing else was done to these animals. Hypoproteinemia was absent. The results were interesting. Definite nephropathy was found in dog 39C, (fig. 12), which had received transfusions of blood for twenty days.

18. Leiter (footnote 17, third reference).

On the other hand, in dog 40C, which had been similarly treated for twenty-two days, the kidneys showed no changes. The ultimate outcome of such lesions is still undetermined, and it is even impossible to state whether or not the renal changes are the result of the experimental procedure.

By far the most extensive gross and microscopic renal lesions in this series of dogs were found in dog 16B, also a control animal. On each of two successive days this dog was given a transfusion of 500 cc. of his own citrated whole blood, reinjected immediately after its withdrawal

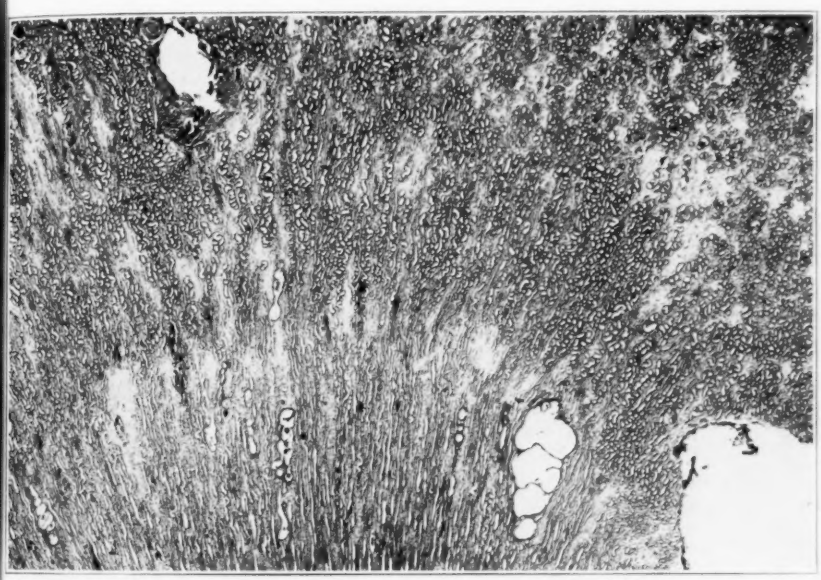

Fig. 10 (dog 16B).—Extreme fibrosis of the inner part of the cortex and upper part of the medulla, in the form of linear scars radiating from the boundary zone. Reduced from a magnification of × 15.

from the heart. The dog died on the second day, in shock. Examination at autopsy disclosed kidneys that were somewhat reduced in size, with partially adherent capsules and surfaces showing depressed irregular scars up to 3 mm. in width, giving a roughly granular appearance. There was marked fibrosis of the inner part of the cortex and the upper part of the medulla, with some scars running all the way through to the depressions on the surface of the kidney. The microscopic features are shown in figures 10 and 11. The marked dilatation of some of the collecting tubules in the upper part of the medulla duplicates the condition described in some of McFadyean's [13] dogs; it is best explained as

the result of obstruction by intertubular fibrosis (fig. 5). Therefore, the advanced stages of the renal lesion described by Barker [15] were found in a control dog of our series.

From these results one may conclude that nothing definite can be concluded as to the actual etiology, or etiologies, of the renal lesions

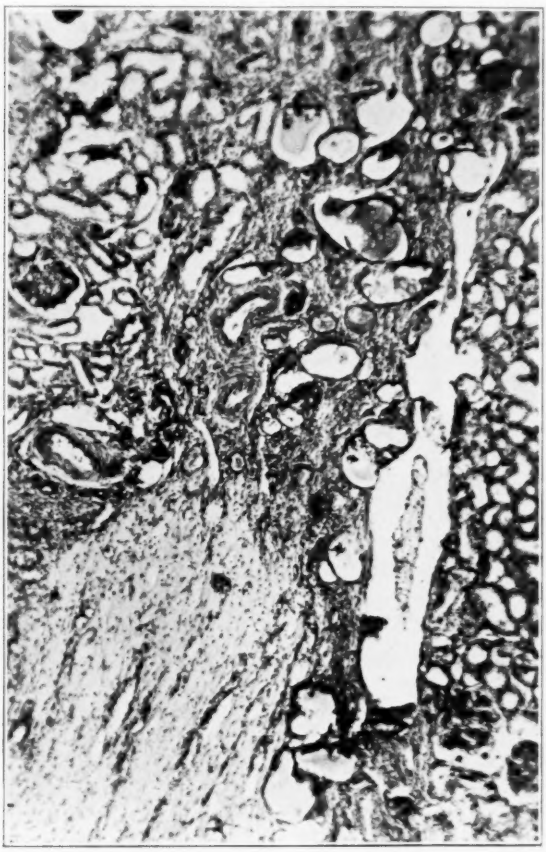

Fig. 11 (dog 16B).—Focal scar in the outer part of the cortex continuing on in the boundary zone and medulla. Only the blood vessels are intact, while tubules and glomerular capsules have largely disappeared except for dilated remnants. Reduced from a magnification of × 70.

in dogs during or following periods of plasmapheresis. Above all, it must be emphasized again that the pathologic picture observed in the kidneys of dogs is entirely unrelated to that which one ordinarily finds

in chronic nephritis or "nephrosis" in human beings. As Bell and Hartzell [7] suggested years ago in connection with similar lesions in the kidneys of rabbits, excretory pyelonephritis in man may be the analog of these renal lesions in laboratory animals. It may also be possible that those rare instances of chronic, truly interstitial nephritis in man,

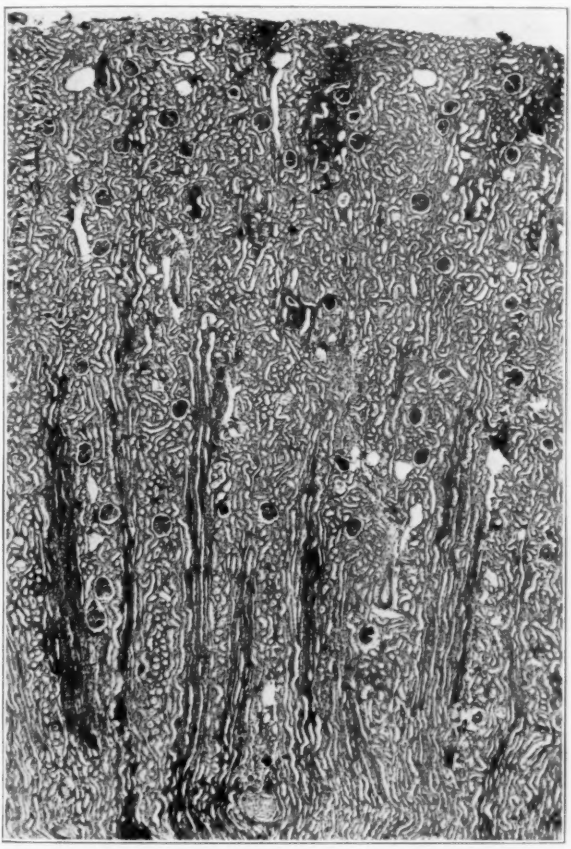

Fig. 12 (dog 39C).—Linear perivascular infiltrates in the inner part of the cortex, with more irregular subcapsular involvement. In these regions the tubules are disappearing by compression atrophy. Reduced from a magnification of × 28.

supposed to result occasionally from acute interstitial nephritis, could be classed in the same group as the focal scarring of the kidneys of laboratory animals. Löwenthal [19] recently reported a case of presumably

19. Löwenthal, K.: Ztschr. f. klin. Med. **105**:420, 1927.

syphilitic, chronic, truly interstitial nephritis. Apart from such isolated rarities, there seems to be no connection between the renal lesions in dogs and chronic nephritis, or "nephrosis," in man. Hence Barker's [15] statement that the secondary contracted kidney (in dogs) following a long-standing low proteinemia "would also suggest an explanation of why most so-called nephrosis cases that escape intercurrent infections die of uremia and at postmortem show scarred and contracted kidneys" has no foundation in fact. Similarly the editorial comment [16] that a "secondarily contracted kidney may well follow a long-standing proteinemia as a result of tubular atrophy and scar tissue replacement" is equally without adequate experimental basis. The problem of the contraction of nephritic or "nephrotic" kidneys in man will be solved only when diffuse glomerulonephritis can be regularly produced in a laboratory animal. It will never be solved by speculation based on erroneous assumptions and uncritical experimental work.

# CHEMISTRY AND METABOLISM IN EXPERIMENTAL YELLOW FEVER IN MACACUS RHESUS

## IV. TOLERANCE TESTS FOR DEXTROSE *

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A number of attempts to determine the impairment or loss of hepatic function by tests for dextrose tolerance have been reported in the literature. Jacobsen,[1] Thannhauser and Pfitzer,[2] Hamman and Hirschman,[3] Friedenson and his co-workers,[4] and John,[5] among others, have applied the test in several diseases by studying the blood sugar at stated intervals after the injection of dextrose or after feeding it by mouth. In many instances a lowered tolerance for sugar has been noted in diseases involving the liver.

In a previous paper,[6] evidence was presented that indicated that in the extreme stages of yellow fever the liver is unable to maintain the blood sugar at its normal level, partly because of a diminished supply of hepatic glycogen. The unusually high level of blood sugar observed in a few moribund animals after meals further suggested that the ability to dispose of administered dextrose was impaired. To secure more direct information concerning this function, tests for sugar tolerance were carried out on *Macacus rhesus*.

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* From the laboratory of the West African Yellow Fever Commission of the International Health Division, Rockefeller Foundation, Lagos, Nigeria.

1. Jacobsen, A. T. B.: Untersuchungen über den Einfluss verschiedener Nahrungsmittel auf den Blutzucker bei normalen, zuckerkranken, und graviden Personen, Biochem. Ztschr. **56**:471, 1913.

2. Thannhauser, S. J., and Pfitzer, H.: Ueber experimentelle Hyperglykämie beim Menschen durch intravenöse Zuckerinjektion, München. med. Wchnschr. **60**:2155, 1913.

3. Hamman, L., and Hirschman, I. I.: Studies on Blood Sugar: Alimentary Hyperglycemia and Glycosuria as a Test of Sugar Tolerance, Arch. Int. Med. **20**:761 (Nov.) 1917.

4. Friedenson, M.; Rosenbaum, M. K.; Thalheimer, E. J., and Peters, J. P.: Cutaneous and Venous Blood-Sugar Curves in Normal Individuals After Insulin and in Liver Disease, J. Biol. Chem. **80**:269, 1928.

5. John, H. J.: Glucose Tolerance, Its Value in Diagnosis, J. Metab. Research **1**:497, 1922.

6. Wakeman, A. M., and Morrell, C. A.: Blood Sugar and Liver Glycogen: III. Chemistry and Metabolism in Experimental Yellow Fever in Macacus Rhesus Monkeys, Arch. Int. Med. **47**:104 (Jan.) 1931.

A dose of 1 Gm. of dextrose per kilogram of body weight was regularly used. Different methods of administering the dextrose were employed. In the case of twenty-three monkeys, of which thirteen were normal and ten infected with yellow fever, the sugar was given by stomach tube. In fifteen monkeys infected with yellow fever and fifteen normal monkeys, dextrose was given intravenously. In two cases a solution of dextrose was injected directly into the lumen of the small intestine.

In many instances bromsulphonphalein tests were carried out in conjunction with the tests for sugar tolerance.

The methods of taking samples of blood and of analysis have been described previously.[6]

The data presented here point to a lowered tolerance for sugar and support the hypothesis that in yellow fever the hepatic lesions render the animal unable to cope in a normal way with an influx of dextrose into the blood stream.

## EXPERIMENTS

*Blood Sugar Following Oral Administration of 1 Gm. of Dextrose per Kilogram of Body Weight.*—Chart 1 presents representative curves for arterial and venous blood sugar for normal animals and for those ill with yellow fever. There is a great variability in the behavior of the normal animals. For example, in *M. rhesus* 11 the level of the blood sugar reached a maximum height thirty-seven minutes after dextrose was taken, and in fifty-two minutes declined below the fasting level, while in *M. rhesus* S1 the blood sugar had not reached a maximum one hundred and twenty minutes after the ingestion of dextrose. In *M. rhesus* 11 the greatest increase observed was only 22 mg. per hundred cubic centimeters. Similar variations occurred in all of the normal animals studied. However, in all of the cases, the curves show that a definite hyperglycemia develops in which the concentrations of dextrose in the arterial blood exceed those in the venous blood.

While in the later stages of yellow fever, monkeys 12 and M40 were treated in a similar way. The distinct difference between the reaction of the sick monkeys and the normal ones to ingested dextrose is the obvious lack of rise in the blood sugar of the sick monkeys as compared with the definite increases in the normal animals. The flat appearance of the curves obtained from *M. rhesus* 12 and M40 may be due to lack of absorption or to rapid storage of sugar in yellow fever. The small arteriovenous differences observed would tend to discredit the latter view. That slow absorption is an important factor is shown by an experiment on *M. rhesus* 13 during the first day of fever. Two and one-fourth hours after the administration by stomach tube of 1 Gm. of dextrose per kilogram, the blood sugar, which had not risen during

the interval, was still at fasting level. Five and one-half hours after the ingestion of dextrose, it had risen to 118 mg. per hundred cubic centimeters from a fasting value of 92 mg. per hundred cubic centimeters. An hour later, when the monkey was killed, of a total of 5 Gm., 2.5 Gm. of dextrose was recovered from the stomach. The intestinal contents were not analyzed. There was no sugar in the urine. It is evident that after six and one-half hours, at least half of a small dose was not absorbed.

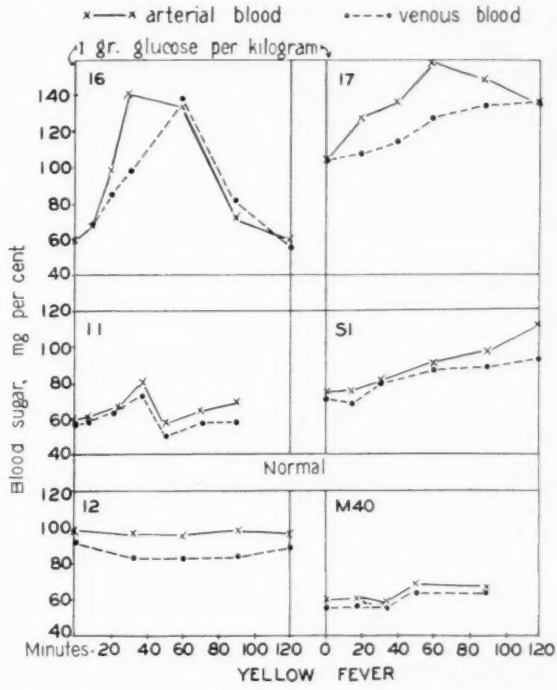


Chart 1.—Curves showing arterial and venous blood sugar in normal monkeys compared with those of moribund monkeys with yellow fever, after the administration by stomach-tube of 1 Gm. of dextrose per kilogram of body weight.

Chart 2 gives the results of a series of tests for sugar tolerance made on different days of the disease.

*Macacus rhesus* 14, a large female weighing 4.49 Kg., was inoculated on December 10 with 1 cc. of blood from a case of yellow fever. On December 11, the temperature was 102.4 F. at 9 a. m., and 102.9 F. at 5 p. m. The animal was strong and fought vigorously. On December 12, the temperature was 105.1 F. at 9 a. m., and 104.9 F.

at 5 p. m. The animal was still vigorous, but less active than on December 11. Urine collected after the experiment contained no sugar and 200 per cent of the bromsulphonphalein. On December 13, the temperature was 103.3 F. at 9 a. m., and 101.3 F. at 5 p. m. The monkey was weak but conscious. At 5 p. m., examination of the blood showed nonprotein nitrogen, 128 mg.; urea nitrogen, 40 mg., and amino-acid nitrogen, 44 mg. per hundred cubic centimeter. On December 14 at 9:30 a. m., the monkey died. Ten cubic centimeters of urine from the bladder contained no sugar and 200 per cent of the bromsulphonphalein.

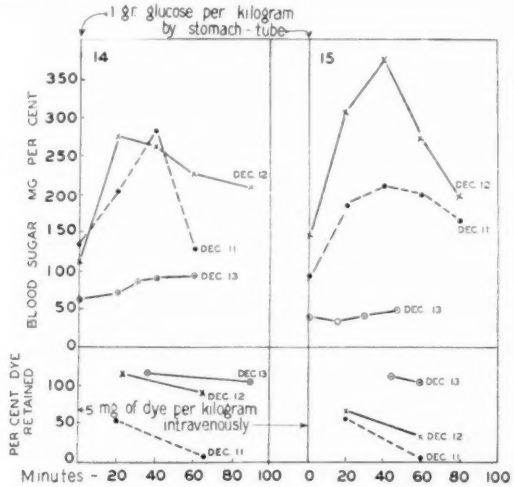


Chart 2.—The changes in the curve for venous sugar of monkeys in the course of yellow fever. In every instance, 1 Gm. of dextrose per kilogram was given by stomach-tube. Curves showing the retention of bromsulphonphalein are presented below for comparison.

*Macacus rhesus* 15, a large male, weighing 3.88 Kg., was inoculated on December 10 with 0.5 cc. of blood infected with yellow fever. On December 11, it had a temperature of 103.5 F. at 9 a. m., and 103.2 F. at 5 p. m. It struggled vigorously when handled. On December 12, the temperature was 104 F. at 9 a. m., and 104.7 F. at 5 p. m. The urine collected after the experiment contained no sugar and 20 per cent of the bromsulphonphalein. The animal feebly resisted handling. On December 13, the temperature was 100 F. at 9 a. m. At 11 a. m., the monkey was moribund, unconscious and prostrate. It died at 12:37 p. m. Three drops of the urine obtained from the bladder at autopsy contained no bromsulphonphalein. At

12:30 p. m., examination of the blood showed: nonprotein nitrogen, 91 mg.; urea nitrogen, 25 mg., and amino-acid nitrogen, 33 mg. per hundred cubic centimeters.

One gram of dextrose per kilogram of body weight in a 6 per cent solution was administered to the monkeys by stomach-tube each day. A few minutes after ingestion, 5 mg. of bromsulphonphalein dye per kilogram was injected intravenously. The curves shown in chart 2 represent the response of the venous blood sugar and the retention of dye in the blood on three successive days. *M. rhesus* 14 retained more of the dye on all three days than did *M. rhesus* 15. This is reflected in the larger excretion in the urine of *M. rhesus* 15. The determination of dye in the urine was carried out by alkalinizing the undiluted urine and comparing it with the blood standard. For convenience, the concentration of dye was expressed in the same terms as that in the blood.

The increase in blood sugar on December 11 in both *M. rhesus* 14 and *M. rhesus* 15 was much greater than in any of the normal monkeys (chart 1), indicating that in these cases there was an abnormality in the curve for sugar as early as the first day after infection. On the second day the return to fasting levels was delayed, while during the third day the curves were flat and presented the same appearance as the venous curves of *M. rhesus* 12 and M40 in chart 1.

To avoid the variations produced by the retention of dextrose in the stomach, the solution of dextrose was injected directly into the lumen of the small intestine of two normal monkeys. About 10 cm. below the pylorus, the duodenum was exposed under aseptic conditions with a minimum of handling; the solution of dextrose was introduced through a fine needle; after the duodenum had been replaced, the abdominal wall was sewn up. Results from these two trials indicated that retention in the stomach was but one factor producing the flat or irregular curves shown in charts 1 and 2. In one case the maximum rise was 50 mg. per hundred cubic centimeters, and in the other 12 mg. The blood sugar did not fall below fasting levels in one and one-half hours, and the general appearance of both curves resembled that of *M. rhesus* M40.

*Intravenous Injections of 1 Gm. of Dextrose per Kilogram of Body Weight.*—In each case the solution of dextrose (from 4 to 7 cc. of a 50 per cent solution was injected into a vein of an arm or the saphenous vein in one minute. Chart 3 represents some of the tests in which venous blood alone was analyzed. It is evident from these curves and those in chart 4, that the reaction of normal monkeys after the intravenous administration of dextrose is far more regular and predictable than that after peroral administration, permitting more accurate evaluation of the disturbances caused by abnormal conditions.

A comparison of the curves for the normal and the sick monkeys reveals a much slower removal of dextrose from the blood of the sick monkeys. After ninety minutes the blood sugar of the normal animals had returned to fasting levels, while it was still high in the animals with yellow fever.

The urine of monkeys 1 and 5 was analyzed for sugar. Forty-five minutes after completion of the test, 10 cc. of urine from normal monkey 1 (chart 3) contained 120 mg. of sugar. In monkey 5, which

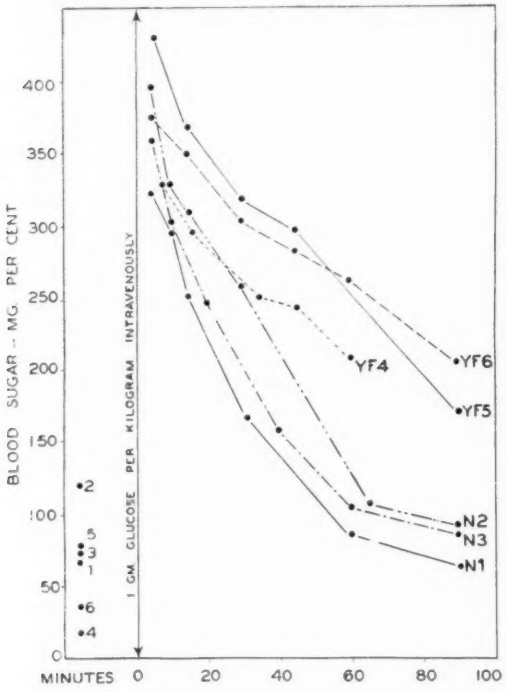


Chart 3.—Curves showing the venous blood sugar of normal monkeys (*N*) and monkeys with yellow fever (*YF*), after the intravenous administration of 1 Gm. of dextrose per kilogram.

had yellow fever, at autopsy and fourteen hours after the last sample of blood was taken, 5 cc. of urine from the bladder contained 130 mg. of sugar. Hence the more rapid fall in blood sugar of the normal animal was not due to greater excretion in the urine.

Some figures obtained from arterial and venous blood of normal and sick monkeys, after the intravenous administration of dextrose, are given in chart 4. Both of the monkeys with yellow fever were prostrate

when the experiment began and died the same night. In monkey 9, at autopsy performed six hours after the completion of the test, 4 cc. of urine contained 150 mg. of sugar.

The results of these tests present two notable features: (1) the decline of blood sugar is slower in the sick monkeys, and (2) in the normal animals the arterial and venous curves cross each other, and they do not cross in the animals with yellow fever.

A part of the large arterial-venous differences encountered directly after injection may be due to the incomplete mixing of the blood. An increase in the venous blood sugar of *M. rhesus* 10 between the six and

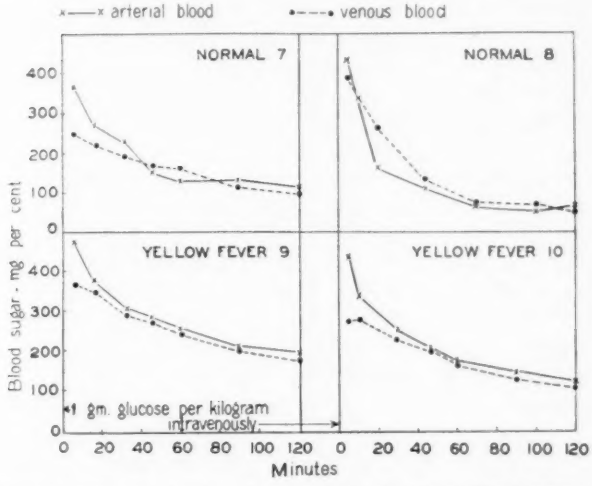


Chart 4.—Curves showing the arterial and venous blood sugar of normal monkeys and monkeys with yellow fever, after the intravenous administration of 1 Gm. of dextrose per kilogram.

sixteen minute interval lends support to this view. Nevertheless, since the tissues are rapidly taking up sugar at this time, as evidenced by the rapid fall in the concentration of blood sugar, large arteriovenous differences are to be expected.

*Analysis of Blood From Various Parts of the Circulation.*—In the early experiments, before the technic of obtaining samples of arterial and venous blood simultaneously was perfected, the arterial blood was taken from one part of the body and the venous blood from another. Later, a check on the concentrations of blood sugar in the various parts of the circulation was made. The results of this investigation have been collected in the accompanying table.

The animal used was a large male *Macacus rhesus* weighing 3.91 Kg. It was given the regular diet at 8 a. m., and when removed from the cage at 9 a. m., he had eaten a part of it. Sixty milligrams of amytal per kilogram of body weight was given intraperitoneally, and the right carotid artery and jugular vein were exposed. The femoral vein and artery on both legs were also dissected out. Blood samples from the different vessels were analyzed for sugar before and after 1 Gm. of dextrose per kilogram of body weight was injected into the right femoral vein. Before injection, blood samples taken not more than a minute apart from the same vessel or different vessels, e. g., femoral vein and jugular vein, femoral artery and carotid artery, yielded almost identical results. The increase in the concentration of sugar in the venous blood between 10:12 a. m. and 10:35 a. m., may be ascribed to absorption from the intestinal tract. Following the injection of sugar there were some large divergences in samples of both venous and arterial blood drawn from different vessels. For example, at 10:45 a. m., blood from the left femoral vein contained 354 mg., while that from the right jugular vein contained 429 mg. per hundred cubic centimeters, a difference of 75 mg. per hundred cubic centimeters. This occurred six minutes after the sugar was injected. The difference is too large for experimental error and is probably due to incomplete mixing of the blood. That such differences do occur emphasizes the necessity of obtaining arterial and venous blood from comparable vessels, such as the femoral vessels of one leg. This precaution was observed in the experiments presented in this article.

If the average concentrations of arterial and venous blood sugar are plotted, the typical crossing and recrossing of the two curves, which were observed after the intravenous injection of dextrose into normal monkeys, becomes apparent.

## COMMENT

The majority of the tests for sugar tolerance, following the oral administration of dextrose to a normal subject, which have been reported in the literature, have two features in common, namely, a rise of the blood sugar to a maximum level in from thirty to forty-five minutes, and a return to normal or subnormal levels in from one to three hours.[7] We had hoped to observe the same phenomena in monkeys and had planned to use these figures as a basis of comparison for the reaction of similar animals ill with yellow fever. The considerable variation in the response of the different normal monkeys to dextrose administered orally made this plan unsatisfactory.

7. Hammon and Hirschman (footnote 3). Friedenson, Rosenbaum, Thalheimer and Peters (footnote 4). John (footnote 5). Gray, H.: Blood Sugar Standards: Normal and Diabetic Persons, Arch. Int. Med. **31**:241 (Feb.) 1923.

Chart 1 shows the rather wide variation in the type of curve obtained, which renders it impossible to interpret with exactness the small changes one would expect to find early in the course of the disease. However, such objections are not so important when dealing with the response of very sick or moribund monkeys, since they show little or no rise in blood sugar after the oral administration of dextrose. The results obtained from the injection of a solution of dextrose into the intestine, and particularly from the experiment with *M. rhesus* 16, indicate that slow absorption is an important factor in producing the flat curves exhibited by *M. rhesus* 12 and M40 in chart 1. If at least

*Results of Test to Determine the Concentration of Blood-Sugar in Various Parts of the Circulation of a Macacus Rhesus*

| Time | Vessel | Blood Sugar Mg. per 100 Cc. |
|---|---|---|
| 10:11 a.m. | Right femoral vein | 72 |
| 10:12 a.m. | Right femoral vein | 71 |
| 10:17 a.m. | Right femoral artery | 89 |
| 10:18 a.m. | Right femoral artery | 89 |
| 10:23 a.m. | Right femoral artery | 87 |
| 10:23 a.m. | Right carotid artery | 87 |
| 10:35 a.m. | Right femoral vein | 85 |
| 10:35 a.m. | Right jugular vein | 87 |
| *10:40-10:41 a.m. | Dextrose injected | ... |
| 10:43 a.m. | Right femoral artery | 545 |
| 10:45 a.m. | Left femoral vein | 354 |
| 10:45 a.m. | Right jugular vein | 429 |
| 10:54 a.m. | Left femoral artery | 329 |
| 10:54 a.m. | Right carotid artery | 340 |
| 11:01 a.m. | Right femoral artery | 280 |
| 11:04 a.m. | Left femoral vein | 281 |
| 11:04 a.m. | Right jugular vein | 270 |
| 11:20 a.m. | Left femoral vein | 218 |
| 11:20 a.m. | Right femoral vein | 216 |
| 11:24 a.m. | Left femoral artery | 202 |
| 11:24 a.m. | Right femoral artery | 178 |
| 11:34 a.m. | Right femoral artery | 131 |
| 11:34 a.m. | Left femoral vein | 165 |
| 11:45 a.m. | Right femoral artery | 108 |
| 11:45 a.m. | Left femoral vein | 144 |
| 11:50 a.m. | Right carotid artery | 100 |
| | Duplicate on same sample | 101 |
| 12:15 p.m. | Right femoral artery | 101 |
| 12:15 p.m. | Left femoral vein | 98 |

* Dextrose injected into right femoral vein.

one half of a small dose of dextrose remains for six and one-half hours in the intestinal tract of a monkey in the early stage of yellow fever, it is probable that a still larger proportion could be found unabsorbed in a prostrate animal.

An indication of progressive failure in ability to handle ingested carbohydrate is shown in the results from *M. rhesus* 14 and 15 (chart 2). Since both monkeys had a short course of fever and survived only four and three days, respectively, after inoculation, the degeneration of the liver must have been rapid. Even on the first day after infection the curves for blood sugar vary in one respect from the normal; the maximum rise, 165 and 115 mg. per hundred cubic centimeters, respectively, in venous blood, is greater than that usually

observed for a normal monkey, from 25 to 85 mg. per hundred cubic centimeters after the same dose. On the following day, which was the first day of fever, further alterations were apparent. The blood sugar of *M. rhesus* 14 rose about 165 mg. per hundred cubic centimeters in the first twenty minutes after injection and then fell rather slowly to 210 mg. per hundred cubic centimeters in ninety minutes. This slow fall of blood sugar following injection in yellow fever is well illustrated in chart 3. The blood sugar of *M. rhesus* 15 rose to 350 mg., an increase of 210 mg. per hundred cubic centimeters above the fasting level, in forty minutes after ingestion, and was still 200 mg. per hundred cubic centimeters at the end of ninety minutes. Both the peak of this curve for blood sugar and the value at the end of one and one-half hours are considerably higher than corresponding values obtained with normal monkeys. While the blood sugar of these two animals during fasting was still within the normal range,[6] a distinct abnormality in the curves for blood sugar after the ingestion of dextrose is evident. On the last day of the experiment, when both animals were obviously ill, curves were obtained that are quite like the others from moribund monkeys shown in chart 1. The curves on both animals are flat, and no maximum is obtained in the first hour after the ingestion of sugar. At this time the blood sugar of both animals during fasting was low, particularly in the case of *M. rhesus* 15, which died several hours before *M. rhesus* 14. In general, the two monkeys showed a tolerance for sugar that decreased with the progress of the disease, while the results of the bromsulphonphalein tests reveal a corresponding decline in the function of the liver, probably due to the hepatic lesions of yellow fever.

The slow fall of blood sugar noted in the experiment with *M. rhesus* 14 on December 12 (chart 2), is confirmed by the results of intravenous injection (chart 3). In the normal animals, blood sugar reached fasting levels in ninety minutes, while in the sick monkeys it remained elevated longer. The slower fall of venous blood sugar in yellow fever is not due to lack of diffusion into the tissues, since arterial-venous differences in these animals are as great as in the normal animals and persist for an even longer time (chart 4); and it is not due to a smaller excretion in the urine, since *M. rhesus* 5 excreted a trifle more than *M. rhesus* 1. Indeed it seems doubtful that excretion was a significant factor in either case. The urine of two sick monkeys not previously mentioned contained only 340 and 305 mg. following injections of 1 Gm. of dextrose per kilogram, and another normal monkey excreted no sugar after the same dose. In this connection, Kleiner [8] found that sugar disappeared from the blood of nephrectomized and normal dogs

8. Kleiner, I. S.: The Disappearance of Dextrose from the Blood After Intravenous Injection, J. Exper. Med. **23**:507, 1916.

at the same rate following intravenous injections. The rapid fall of blood sugar immediately after intravenous injections is best accounted for by distribution to the tissues, and the large arterial-venous differences support the view.

Briefly, the sequence of events following the intravenous injection of dextrose is: (1) a rapid fall of the blood sugar brought about by diffusion of dextrose into muscle, skin, liver and other tissues; (2) a redistribution of the sugar from muscle, skin and subcutaneous tissues to other organs, notably the liver, there to be used in the formation of glycogen; (3) further formation of glycogen by the muscles, with a coincident withdrawal of sugar from the blood.

The alterations of arterial and venous blood sugar are consistent with this explanation. The remarkable feature of the sugar curves presented in chart 4 is the crossing of the arterial and venous curves in the normal animal and the fact that they do not cross in the animals with yellow fever. The significance of this difference is that in yellow fever the liver is capable of forming little or no glycogen, and hence the sugar is not withdrawn from the blood so rapidly as in the normal animals. This assumption is validated by finding only traces of glycogen in the livers of monkeys dying with yellow fever.[6] In normal monkey 7 (chart 4), the immediate distribution of dextrose to the tissues is evidenced by the large positive differences between the values for arterial and venous blood sugar obtained in the first forty minutes after injection. A similar reaction occurred in monkey 9, ill with yellow fever. However, after forty minutes the arteriovenous differences in monkey 7 became negative, while in monkey 9 they remained positive throughout the experiment. During the second forty minutes of the experiment with monkey 7, sugar was being removed from the muscles by the blood and presumably carried to the liver for the formation of glycogen. Since glycogenesis in the liver of monkey 9 was proceeding slowly or not at all, the reversal of arteriovenous differences in blood sugar was not evident. Still later in the experiment, when the blood sugar was approaching fasting levels, glycogenesis made itself evident in the muscles, and there was a second reversal of the arteriovenous differences.

Thus the outstanding distinctions between the reactions to the tests for sugar tolerance of normal monkeys and those ill with yellow fever are the slower fall of the blood sugar level and the lack of reversal of the arteriovenous differences in blood sugar in the sick animals. Both of these variations can be accounted for by the inability of the liver to form glycogen.

## SUMMARY

1. The response of the blood sugar of normal monkeys to dextrose administered perorally is irregular. Monkeys very ill with yellow fever show practically no increase in blood sugar after the ingestion of 1 Gm.

of dextrose per kilogram, chiefly because in this condition sugar is absorbed extremely slowly, if at all, from the alimentary canal.

2. Tolerance for sugar is diminished in yellow fever before the monkeys become prostrate.

3. Dextrose injected intravenously is not so rapidly removed from the blood of monkeys ill with yellow fever as from the blood of normal monkeys.

4. In normal monkeys, after the intravenous injection of dextrose, accelerated glycogenesis in the liver is manifested by a crossing of the curves for arterial and venous blood sugar as the initial hyperglycemia subsides. Crossing of the curves is absent in yellow fever, indicating loss of hepatic function.

# THE RÔLE OF ARTICHOKES IN THE DIET OF THE DIABETIC PATIENT*

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At various times Jerusalem artichokes have been advocated in the diet of the diabetic patient. The tuber is rich in inulin, which on hydrolysis yields levulose, a monosaccharid to which is attributed the peculiar power of easier assimilation than dextrose. Joslin [1] expressed the belief that this may be due to the conversion of a portion of the levulose to fat or to a more active stimulation of the production of insulin.

A word may not be amiss here concerning the name and history of the plant. The following information is contained in an article by Shoemaker.[2] The Jerusalem artichoke, *Helianthus tuberosus* L., is widely known but little used in the United States. Champlain found the tuber growing in the gardens of the Indians at Mallebarre (now Nauset Harbor, Cape Cod, Mass.) on July 21, 1604. Lescarbot, a companion of Champlain, probably introduced it into France. Plants similar in growth and flowering to many of the present day varieties grown at Washington, D. C., were described and pictured by Colonna in 1616 as occurring in the garden of Cardinal Farnese at Rome. The name, "Jerusalem artichoke," has been a source of continual comment, since it is neither descriptive nor true. For many years the first word has been explained as an English corruption of the Italian word "girasole" meaning, at present, sunflower. The resemblance in flavor of the Jerusalem artichoke to the true artichoke has accounted for the latter half of the name.

The plant is widely distributed throughout the United States. Its range of growth is usually given as from New York to Minnesota, and southward to Georgia and Arkansas. More recently its cultivation has been introduced into Colorado, Oregon and California.

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† Research fellow under a grant from Pabst Dietary Products, Inc.

1. Joslin, E. P.: The Treatment of Diabetes Mellitus, ed. 4, Philadelphia, Lea & Febiger, pp. 630-631.

2. Shoemaker, D. N.: The Jerusalem Artichoke as a Crop Plant, Tech. Bull. no. 33, U. S. Dept. of Agriculture, Washington, D. C., October, 1927.

In spite of repeated investigations, divergencies still exist as to the nature and relative proportions of the carbohydrates found in the tuber. This is probably due to the fact that the various analyses have been made on tubers that have been collected at different seasons of the year and stored for varying lengths of time. Any one who is at all familiar with this vegetable knows that immediately after frost there is a marked increase in its sugar content. Prior to that time, the raw tuber has an insipid taste; as soon as frost occurs, it becomes sweet and acquires an improved flavor. The most complete report on the nature of the carbohydrates is the recent contribution of Thaysen, Bakes and Green [3] who concluded that the unripe, autumn-gathered tuber contains a large amount of an insoluble, nonfermentable carbohydrate apparently identical with inulin, which disappears almost completely toward spring, giving way to increased proportions of the more soluble

TABLE 1.—*Percentage of Distribution of Carbohydrates in the Jerusalem Artichoke (Helianthus tuberosus L.) Calculated on the Basis of the Total Carbohydrates Present* *

| Tubers Harvested | Inulin and Pseudo-Inulin, per Cent | Simpler Carbohydrates, per Cent |
|---|---|---|
| Sept.-Oct., 1924† | 84.66‡ | 15.34 |
| November, 1923 | 41.44 | 58.56 |
| March, 1924 | 1.02 | 98.98 |

* From Thaysen, Bakes and Green (footnote 3).
† Analysis taken from Tanret (footnote 4).
‡ Includes inulenin, helianthenin and synanthrin, carbohydrates similar to inulin, but not separated by the analyses of Thaysen, Bakes and Green.

carbohydrates that are already present to a slight extent in the autumn tuber. Table 1 gives analyses taken from this paper to show how changes occur in the carbohydrates with the ripening of the tuber.

The question of the fermentability of inulin and related carbohydrates should receive some consideration, as fermentation may play an important part in the assimilability of the more complex carbohydrates of the artichoke. Although inulin itself is unfermentable by yeast, Tanret [4] reported that it was fermented when present in a solution of already fermenting carbohydrates, an observation that was confirmed by Thaysen, Bakes and Green.[3] Moreover, the latter investigators found that a comparatively mild autoclaving without the use of acid hydrolysis is sufficient to render inulin fermentable by yeast.

Thus, the literature shows that tubers of Jerusalem artichokes that have been allowed to remain in the ground until the plant has been

3. Thaysen, A. C.; Bakes, W. E., and Green, B. M.: On the Nature of the Carbohydrates Found in the Jerusalem Artichoke, Biochem. J. **23**:444, 1929.

4. Tanret: Bull. Soc. chim. de France **9**:622, 1893 (cited by Thaysen, Bakes, and Green, footnote 3).

killed by frost contain a relatively high percentage of digestible carbohydrates, that autoclaving will hydrolyze some of the higher carbohydrates and that fermentation of inulin by yeast may occur in the presence of fermenting carbohydrates. From the latter facts, it seems probable that ordinary cooking may render digestible some of the more complex carbohydrates that are left in partially ripened tubers, and that inulin may behave in the presence of bacterial fermentation of other carbohydrates as it does with the fermentation by yeast under such conditions.

In 1923, Joslin and Root [5] reported that the feeding of 15 Gm. of inulin in the form of Jerusalem artichokes did not produce glycosuria in the diabetic person. Root and Baker [6] obtained beneficial results in a group of patients over a period of six months and concluded that, in the amounts given, the Jerusalem artichoke could be added to the diets without increasing the glycosuria, when it was present, or producing it when previously absent. In certain cases, when the tubers were substituted for the other carbohydrates in the diet, glycosuria disappeared. Carpenter and Root [7] studied intensively the effect of the Jerusalem artichoke on a person with diabetes mellitus when the tuber furnished half of the carbohydrate in the diet. This case is also mentioned elsewhere by Joslin,[1] and both writers were enthusiastic about the utilization of the carbohydrates of the artichoke by the diabetic patient. However, Westcott and Wise,[8] using one subject over a period of eighteen days, reported negative results and concluded that dried artichokes have no advantage as a diabetic food.

Our interest in the subject was aroused by the reports of several physicians that they had found the Jerusalem artichoke to be of tremendous value in the dietetic control of diabetes. The controversial nature of the reports in the literature previously cited convinced us of the importance of further investigation.

## EXPERIMENTAL DATA

Beginning in January, 1930, the effect of feeding artichokes to a group of diabetic patients in the Colorado General Hospital [9] of the University of Colorado School of Medicine was studied. The procedure adopted was to place a patient

5. Joslin, E. P., and Root, H. F.: Levulose and the Diabetic Metabolism, J. A. M. A. **80**:1727 (June 9) 1923.

6. Root, H. F., and Baker, M. L.: Inulin and Artichokes in the Treatment of Diabetes, Arch. Int. Med. **36**:126 (July) 1925.

7. Carpenter, T. M., and Root, H. F.: The Utilization of Jerusalem Artichokes by a Patient with Diabetes, Arch. Int. Med. **42**:64 (July) 1928.

8. Westcott, L. E., and Wise, E. C.: Failure of a Diabetic Patient to Utilize Dried Artichoke Powder, Arch. Int. Med. **44**:362 (Sept.) 1929.

9. During the period of hospitalization all patients were on the medical service of Dr. Charles N. Meader.

on an adequate diabetic diet and to adjust the intake of carbohydrate so that a definite but slight glycosuria of moderate variation would result. Although the accomplishment of this might require a number of days, or even as long as three or four weeks, every care was made to establish the patient's tolerance before proceeding with the feeding of the artichokes. Not until a glycosuria with a variation of only a few grams in the daily average output of sugar was obtained could it be considered safe to study the effect of artichokes in the diet. Then they were introduced either by substituting the carbohydrates of the artichoke for other carbohydrates or by superimposing them on the carbohydrate already present. None of the patients received insulin at any time during the experimental period. Thus, by the method adopted, it was possible to determine, from a study of any change that might occur in the amount of sugar excreted when the artichokes were fed, whether or not they had had any influence on the subject's tolerance for carbohydrates.

The artichoke products [10] used had been prepared and preserved for commercial distribution by different processes. All were made from tubers that had remained in the ground until the plants had been killed by frost. Several kinds of preparations were fed in order to furnish variety to the patient. Puree, which consisted of the ground artichoke preserved in its own juice after sterilization

TABLE 2.—*Analyses of Jerusalem Artichoke Products* *

| | Dried Slices, per Cent | Puree, per Cent | Flakes, per Cent |
|---|---|---|---|
| Moisture | 3.81 | 77.20 | 2.08 |
| Fat | 0.43 | 0.60 | 30.92 |
| Carbohydrate | 67.27 | 17.20 | 52.20 |
| Protein | 7.59 | 2.20 | 4.41 |
| Mineral salts | 7.03 | 1.50 | 3.15 |
| Cellulose and undetermined | 13.87 | 1.30 | 7.24 |

* Furnished by Pabst Dietary Products, Inc.

with steam, dehydrated slices, dried in vacuo at moderately low temperatures, and artichoke flakes, similar to potato flakes and made by cooking the freshly sliced tubers in cottonseed oil, were used. Table 2 gives analyses of the Jerusalem artichoke products as furnished by the manufacturer.

The flakes were fed as received. The puree was served as a soup, or as a vegetable after seasoning with salt, pepper and butter, and cooking down to a more solid consistency. The dried slices were made palatable by steaming, or by cooking in a casserole, with such foods as cheese, shrimp, meat or various vegetables, and by appropriate seasoning. The flakes were found to be the most palatable, and the patients were able to consume more artichokes in this form without discomfort than when the other products were eaten.

During the first few days of the feeding of artichokes, the patients experienced considerable abdominal distress from the formation of gas. If the amount of artichokes in the diet was not increased too rapidly, these symptoms were ameliorated to a great extent and, subsequently, it was usually possible to give large quantities of artichoke products, particularly if the greater amount was in the form of flakes, without a recurrence of marked discomfort.

A careful record was made of the intake of food of each patient, and specimens of urine were collected at intervals of twenty-four hours throughout the experimental period. Quantitative determinations of the sugar excreted were made

10. All of the artichoke products were supplied by Pabst Dietary Products, Inc.

by the Benedict method.[11] The urine was tested daily for acetone by the Legal method and for diacetic acid by the Gerhardt method. Total nitrogen was determined by the Kjeldhal method, both as a check on whether or not we had received a complete twenty-four hour specimen and so that we might later refer to the metabolism of nitrogen, if the artichokes were found to have any influence on the diabetic condition of the patient. At frequent intervals, blood was drawn before breakfast, and sugar was determined by the procedure of Folin-Wu[12] as modified for use with the Peebles-Lewis colorimeter.[13]

The patients studied were recruited from the outpatient department of the hospital, and only those from whom satisfactory cooperation could be expected were used. The cases varied from the mild to the moderate type of diabetes. The following representative cases are reported.

## REPORT OF CASES

Case 1.—G. W., a boy, aged 15, weighing 147 pounds (66.7 Kg.), had had influenza at 13, followed by "kidney trouble," defective vision and puffiness below the eyes. In March, 1929, he fell from a ladder on a school playground, at which time he wrenched his right side and bruised the right side of his face, but suffered no loss of consciousness. Soon after the fall he noticed the first symptoms of diabetes, namely, polyuria, polydipsia and marked loss of weight. No treatment was instituted until September, when he was hospitalized. Under a regulated diet and the administration of insulin, he responded satisfactorily and was discharged after one month. At home he became careless in controlling his diet. When he first came under the care of Dr. Stein early in November, he was living on a normal diet, taking 20 units of insulin every day. The blood sugar was 272 mg. per hundred cubic centimeters, and the twenty-four hour specimen of urine showed 227 Gm. of dextrose. On a diet of 50 Gm. of carbohydrate, 75 of protein and 150 of fat the glycosuria was controlled in six days, and the necessity of using insulin was eliminated in ten more days. When the patient entered the Colorado General Hospital on Jan. 7, 1930, for observation during the feeding of artichokes, the urine was sugar-free. The diet was increased gradually to produce glycosuria. On February 16, he was getting 400 Gm. of carbohydrate, 80 of protein and 120 of fat, and was excreting such a fairly constant amount of dextrose daily that he was considered ready for study. Table 3 gives data concerning the diet and laboratory observations in this case during the experimental period. Subsequent to the discharge from the hospital, this patient was observed in the outpatient department of the School of Medicine and continued in first class condition without the administration of insulin for the several weeks that followed.

Case 2.—In A. R., a woman, aged 25, weighing 106 pounds (48.1 Kg.), sugar was found in the urine during an influenza attack a year previously, but no treatment was instituted by the attending physician. During the preceding few months

11. Benedict, S. R.: A Method for the Estimation of Reducing Sugars, J. Biol. Chem. **9**:57, 1911.

12. Folin, O., and Wu, H.: A System of Blood Analysis: Supplement I. A Simplified and Improved Method for Determination of Sugar, J. Biol. Chem. **41**:367, 1920.

13. Peebles, A. R., and Lewis, R. C.: A Simple and Accurate Colorimeter for Clinical Use, J. A. M. A. **70**:679 (March 9) 1918. Lewis, R. C.: Two Improved Designs of the Peebles-Lewis Clinical Colorimeter, J. Lab. & Clin. Med. **16**:914 (June) 1931.

TABLE 3.—*Data Concerning the Diet and Laboratory Observations in G. H.*

| | | Urine | | | | Diet | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Carbohydrate | | |
| Date, 1930 | Weight, Pounds | Volume, Cc. | Nitrogen, Gm. | Sugar, Gm. | Blood Sugar, Mg. | Protein, Gm. | Fat, Gm. | Total, Gm. | Artichoke, Gm. | Calories |
| 2/15 | 142 | 2,070 | 7.9 | 3.7 | ... | 80 | 120 | 400 | ..... | 3,000 |
| 2/16 | 142 | 2,545 | 9.2 | 4.8 | ... | 80 | 120 | 400 | ..... | 3,000 |
| 2/17 | 142 | 2,330 | 7.9 | 3.1 | ... | 80 | 120 | 400 | ..... | 3,000 |
| 2/18 | 142 | 2,360 | 10.6 | 2.9 | ... | 80 | 120 | 400 | ..... | 3,000 |
| 2/19 | 142 | 1,420 | 6.7 | 1.7 | 88 | 80 | 120 | 400 | 20 Subst. | 3,000 |
| 2/20 | 142 | 2,140 | 9.1 | 3.8 | ... | 80 | 120 | 400 | 20 Subst. | 3,000 |
| 2/21 | 143 | 2,075 | 6.5 | 6.9 | ... | 80 | 120 | 400 | 20 Subst. | 3,000 |
| 2/22 | 143 | 1,565 | 8.3 | 2.8 | ... | 80 | 120 | 400 | 20 Subst. | 3,000 |
| 2/23 | 143 | 3,180 | 11.2 | 3.1 | ... | 80 | 120 | 400 | 40 Subst. | 3,000 |
| 2/24 | 143 | 1,565 | 5.5 | 3.5 | ... | 80 | 120 | 400 | 40 Subst. | 3,000 |
| 2/25 | 143 | 2,680 | 7.5 | 3.3 | 98 | 80 | 120 | 400 | 40 Subst. | 3,000 |
| 2/26 | 144 | 2,010 | 8.3 | 4.1 | ... | 80 | 120 | 400 | 40 Subst. | 3,000 |
| 2/27 | 144 | 2,210 | 9.3 | 3.1 | ... | 80 | 120 | 400 | 70 Subst. | 3,000 |
| 2/28 | 144 | 2,475 | 8.5 | 8.4 | ... | 80 | 120 | 400 | 70 Subst. | 3,000 |
| 3/ 1 | 145 | 2,325 | 9.3 | 2.5 | ... | 80 | 120 | 400 | 70 Subst. | 3,000 |
| 3/ 2 | 145 | 2,015 | 8.1 | 2.7 | ... | 80 | 120 | 400 | 100 Subst. | 3,000 |
| 3/ 3 | 145 | 2,280 | 8.5 | 4.3 | 107 | 80 | 120 | 400 | 100 Subst. | 3,000 |
| 3/ 4 | 144 | 1,755 | 5.6 | .... | ... | 80 | 120 | 400 | 100 Subst. | 3,000 |
| 3/ 5 | 144 | 2,380 | 8.1 | ..... | ... | 80 | 120 | 400 | ..... | 3,000 |
| 3/ 6 | 144 | 2,490 | 8.1 | 6.6 | ... | 80 | 120 | 400 | ..... | 3,000 |
| 3/ 7 | 144 | 2,355 | 8.7 | 10.0 | ... | 80 | 120 | 400 | ..... | 3,000 |
| 3/ 8 | 144 | 2,195 | 7.1 | 6.0 | ... | 80 | 120 | 420 | 20 Added | 3,080 |
| 3/ 9 | 146 | 3,355 | 9.2 | 32.1 | ... | 80 | 120 | 420 | 20 Added | 3,080 |
| 3/10 | 146 | 2,795 | 8.6 | 10.0 | ... | 80 | 120 | 420 | 20 Added | 3,080 |
| 3/11 | 146 | 2,735 | 10.1 | 41.1 | 140 | 80 | 120 | 420 | 20 Added | 3,080 |
| 3/12 | 144 | 2,940 | 10.2 | 67.0 | ... | 80 | 120 | 420 | 20 Added | 3,080 |
| 3/13 | 145 | 3,000 | 8.4 | 44.3 | 170 | 80 | 120 | 420 | 20 Added | 3,080 |
| 3/14 | 145 | 3,075 | 9.0 | 91.5 | ... | 80 | 120 | 420 | 20 Added | 3,080 |
| 3/15 | 145 | 1,420 | 8.7 | 26.0 | 168 | 80 | 120 | 400 | ..... | 3,000 |
| 3/16 | 145 | 2,520 | 10.2 | 40.4 | ... | 80 | 120 | 400 | ..... | 3,000 |
| 3/17 | 145 | 2,555 | 7.0 | 77.0 | 178 | 80 | 120 | 400 | ..... | 3,000 |
| 3/18 | 145 | 2,445 | .... | 56.6 | ... | 80 | 120 | 400 | 100 Subst. | 3,000 |
| 3/19 | 145 | 4,526 | 16.7 | 132.1 | 212 | 80 | 120 | 400 | 100 Subst. | 3,000 |
| 3/20 | 145 | 2,010 | 6.5 | 60.6 | ... | 80 | 120 | 400 | 100 Subst. | 3,000 |
| 3/21 | 145 | 2,060 | 9.0 | 60.3 | 218 | 80 | 120 | 400 | 100 Subst. | 3,000 |
| 3/22 | 145 | 1,655 | 7.9 | 46.3 | ... | 80 | 120 | 400 | 100 Subst. | 3,000 |
| 3/23 | 145 | 2,085 | 8.9 | 64.6 | ... | 80 | 120 | 400 | 100 Subst. | 3,000 |
| 3/24 | 146 | 1,660 | 9.0 | 74.8 | 208 | 80 | 120 | 400 | 100 Subst. | 3,000 |
| 3/25 | 145 | 2,240 | 8.9 | 87.2 | ... | 80 | 120 | 400 | 100 Subst. | 3,000 |
| 3/26 | 145 | ..... | .... | .... | 228 | 80 | 120 | 400 | 200 Subst. | 3,000 |
| 3/27 | 145 | 1,640 | 7.4 | 30.4 | ... | 80 | 120 | 400 | 200 Subst. | 3,000 |
| 3/28 | 145 | 1,540 | 7.0 | 17.6 | 210 | 80 | 120 | 400 | 200 Subst. | 3,000 |
| 3/29 | 145 | 1,710 | 7.2 | 33.8 | ... | 80 | 120 | 400 | 200 Subst. | 3,000 |
| 3/30 | 145 | 1,310 | 6.8 | 41.2 | ... | 80 | 120 | 400 | 200 Subst. | 3,000 |
| 3/31 | 145 | 2,520 | 5.4 | 37.1 | 190 | 80 | 120 | 400 | 200 Subst. | 3,000 |
| 4/ 1 | 145 | 1,425 | 5.6 | 20.1 | ... | 80 | 120 | 400 | 200 Subst. | 3,000 |
| 4/ 2 | 145 | 2,420 | 8.8 | 81.9 | 220 | 80 | 120 | 400 | 200 Subst. | 3,000 |
| 4/ 3 | 145 | 1,610 | 6.5 | 61.1 | ... | 80 | 120 | 400 | 200 Subst. | 3,000 |
| 4/ 4 | 145 | 2,120 | 6.2 | 119.6 | 236 | 80 | 120 | 350 | ..... | 2,800 |
| 4/ 5 | 145 | 1,790 | 8.6 | 115.8 | ... | 80 | 120 | 350 | ..... | 2,800 |
| 4/ 6 | 145 | 2,230 | 10.8 | 99.0 | ... | 80 | 120 | 300 | ..... | 2,600 |
| 4/ 7 | 145 | 2,040 | 7.1 | 113.9 | ... | 80 | 120 | 300 | ..... | 2,600 |
| *4/ 8 | 144 | 2,365 | 6.5 | 129.0 | 214 | 80 | 120 | 300 | ..... | 2,600 |
| 4/ 9 | 143 | 2,395 | 9.7 | 145.3 | ... | 80 | 120 | 300 | ..... | 2,600 |
| 4/10 | 144 | 2,020 | 12.2 | 145.9 | 252 | 80 | 120 | 250 | ..... | 2,400 |
| 4/11 | 144 | 1,800 | 12.9 | 137.3 | ... | 80 | 120 | 250 | ..... | 2,400 |
| 4/12 | 143 | 1,635 | 16.0 | 81.4 | 180 | 80 | 120 | 150 | ..... | 2,000 |
| *4/13 | 141 | 1,855 | 15.0 | 23.8 | ... | 80 | 120 | 75 | ..... | 1,700 |
| 4/14 | 140 | 1,835 | 10.9 | 24.4 | 210 | 80 | 120 | 75 | ..... | 1,700 |
| 4/15 | 138 | 1,560 | 11.6 | 8.4 | ... | 80 | 120 | 75 | ..... | 1,700 |
| 4/16 | 138 | 1,905 | 10.4 | 10.2 | ... | 80 | 120 | 75 | ..... | 1,700 |
| *4/17 | 137 | 2,610 | 7.4 | 14.9 | ... | 80 | 120 | 75 | ..... | 1,700 |
| 4/18 | 137 | 2,285 | 13.6 | 8.2 | ... | 80 | 150 | 75 | ..... | 1,970 |
| *4/19 | 137 | 2,900 | 18.9 | 23.5 | 184 | 80 | 150 | 75 | ..... | 1,970 |
| 4/20 | 137 | 2,840 | 16.1 | 14.4 | ... | 80 | 150 | 75 | ..... | 1,970 |
| 4/21 | 137 | 2,040 | 13.9 | 12.2 | ... | 80 | 150 | 75 | ..... | 1,970 |
| 4/22 | 136 | 1,950 | 13.5 | Trace | ... | 75 | 150 | 50 | ..... | 1,850 |
| 4/23 | 135 | 2,350 | 13.5 | .... | ... | 75 | 150 | 50 | ..... | 1,850 |
| 4/24 | 135 | 2,445 | 12.2 | .... | ... | 75 | 150 | 50 | ..... | 1,850 |
| 4/25 | 135 | 1,800 | 12.3 | .... | 190 | 75 | 150 | 50 | ..... | 1,850 |
| 4/29 | ... | ..... | .... | .... | 116 | .. | ... | ... | ..... | ..... |

* Acetone present in urine (tests were made daily).

TABLE 4.—*Data Concerning the Diet and Laboratory Observations in A. R.*

| | | Urine | | | | Diet | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Carbohydrate | | |
| Date, 1930 | Weight, Pounds | Volume, Cc. | Nitrogen, Gm. | Sugar, Gm. | Blood Sugar, Mg. | Protein, Gm. | Fat, Gm. | Total, Gm. | Artichoke, Gm. | Calories |
| 2/22 | 110 | 1,240 | .... | 7.6 | ... | 50 | 150 | 50 | ..... | 1,750 |
| 2/23 | 109 | 930 | 3.3 | 2.4 | ... | 50 | 150 | 50 | ..... | 1,750 |
| †2/24 | 106 | 1,555 | 7.1 | 2.6 | 116 | 50 | 150 | 50 | ..... | 1,750 |
| †2/25 | 106 | 1,720 | 6.8 | 1.8 | ... | 50 | 150 | 50 | ..... | 1,750 |
| †2/26 | 105 | 1,530 | 5.8 | 1.7 | ... | 50 | 150 | 60 | ..... | 1,790 |
| †2/27 | 107 | 1,540 | 6.0 | 2.3 | ... | 50 | 150 | 60 | ..... | 1,790 |
| *†2/28 | 107 | 2,185 | 5.9 | .... | ... | 50 | 150 | 60 | ..... | 1,790 |
| *†3/ 1 | 107 | 2,475 | 7.2 | 1.9 | ... | 50 | 150 | 60 | 20 Subst. | 1,790 |
| *†3/ 2 | 107 | 2,460 | 5.5 | 1.8 | ... | 50 | 150 | 60 | 20 Subst. | 1,790 |
| †3/ 3 | 106 | 3,115 | 4.5 | .... | 113 | 50 | 150 | 60 | 30 Subst. | 1,790 |
| 3/ 4 | 106 | 2,015 | 5.4 | 16.7 | ... | 55 | 150 | 175 | ..... | 1,790 |
| 3/ 5 | 107 | 2,355 | 3.1 | 3.1 | ... | 50 | 150 | 60 | ..... | 2,270 |
| 3/ 6 | 108 | 3,055 | 4.7 | 2.3 | ... | 50 | 150 | 80 | 20 Added | 1,790 |
| 3/ 7 | 108 | 2,205 | 4.6 | .... | ... | 50 | 150 | 80 | 20 Added | 1,870 |
| 3/ 8 | 108 | 2,110 | 4.7 | .... | ... | 50 | 150 | 80 | 20 Added | 1,870 |
| †3/ 9 | 108 | 2,815 | 4.8 | .... | ... | 50 | 150 | 80 | 20 Added | 1,870 |
| †3/10 | 109 | 1,905 | 4.5 | .... | ... | 50 | 150 | 100 | 40 Added | 1,870 |
| †3/11 | 109 | 2,805 | 3.8 | .... | 126 | 50 | 150 | 100 | 40 Added | 1,950 |
| †3/12 | 108 | 1,955 | 4.0 | .... | ... | 50 | 150 | 140 | 80 Added | 1,950 |
| 3/13 | 110 | 2,835 | 5.1 | .... | 107 | 50 | 150 | 140 | 80 Added | 2,110 |
| †3/14 | 111 | 2,135 | 3.5 | .... | ... | 50 | 150 | 140 | 80 Added | 2,110 |
| 3/15 | 110 | 2,085 | 4.5 | .... | 109 | 50 | 150 | 160 | 100 Added | 2,110 |
| 3/16 | 111 | 1,975 | 4.3 | .... | ... | 50 | 150 | 160 | ..... | 2,190 |
| 3/17 | 111 | 2,935 | 3.8 | 2.0 | 124 | 50 | 150 | 180 | ..... | 2,190 |
| 3/18 | 111 | 3,450 | .... | 1.9 | ... | 50 | 150 | 190 | ..... | 2,270 |
| 3/19 | 110 | 2,620 | 4.5 | .... | 130 | 50 | 150 | 200 | ..... | 2,310 |
| 3/20 | 111 | 2,725 | 4.4 | .... | ... | 50 | 150 | 200 | ..... | 2,350 |
| 3/21 | 110 | 3,300 | 4.6 | .... | 148 | 50 | 150 | 200 | ..... | 2,350 |
| 3/22 | 110 | 3,210 | 5.5 | 5.6 | ... | 50 | 150 | 210 | ..... | 2,350 |
| 3/23 | 110 | 3,200 | 6.2 | 8.2 | ... | 50 | 150 | 220 | ..... | 2,390 |
| 3/24 | 110 | 3,040 | 5.6 | Trace | 156 | 50 | 150 | 220 | ..... | 2,430 |
| 3/25 | 110 | 2,095 | 5.8 | .... | ... | 50 | 150 | 220 | ..... | 2,430 |
| 3/26 | 111 | 2,025 | 3.5 | .... | 138 | 50 | 150 | 220 | ..... | 2,430 |
| 3/27 | 112 | 2,250 | 3.9 | .... | ... | 50 | 150 | 220 | 100 Subst. | 2,430 |
| 3/28 | 111 | 1,540 | 3.3 | .... | 124 | 50 | 150 | 220 | 100 Subst. | 2,430 |
| 3/29 | 112 | 3,180 | 4.0 | .... | ... | 50 | 150 | 220 | 100 Subst. | 2,430 |
| 3/30 | 110 | 1,880 | 3.7 | .... | ... | 50 | 150 | 220 | ..... | 2,430 |
| 3/31 | 110 | 2,025 | 4.3 | Trace | 127 | 50 | 150 | 320 | 100 Added | 2,430 |
| 4/ 1 | 111 | 2,760 | 3.9 | .... | ... | 50 | 150 | 320 | 100 Added | 2,830 |
| 4/ 2 | 111 | 2,025 | 4.4 | 3.6 | 142 | 50 | 150 | 320 | 100 Added | 2,830 |
| *4/ 3 | 111 | 970 | 3.6 | 10.2 | ... | 50 | 150 | 320 | 100 Added | 2,830 |
| 4/ 4 | 111 | 2,400 | 4.8 | 17.0 | 144 | 54 | 181 | 252 | ..... | 2,853 |
| 4/ 5 | 112 | 1,700 | 4.8 | 7.2 | ... | 54 | 181 | 252 | ..... | 2,853 |
| 4/ 6 | 111 | 2,180 | 4.3 | 3.6 | ... | 54 | 181 | 200 | ..... | 2,645 |
| 4/ 7 | 111 | 1,690 | 4.4 | 1.4 | ... | 54 | 181 | 200 | ..... | 2,645 |
| 4/ 8 | 110 | 3,125 | 5.8 | Trace | 172 | 54 | 181 | 200 | ..... | 2,645 |
| 4/ 9 | 110 | 2,655 | 6.8 | 24.1 | ... | 54 | 181 | 200 | ..... | 2,645 |
| 4/10 | 111 | 2,635 | 5.4 | 3.1 | 188 | 50 | 125 | 150 | ..... | 1,925 |
| *4/11 | 111 | 2,585 | 5.0 | 13.9 | ... | 54 | 125 | 200 | ..... | 2,141 |
| 4/12 | 110 | 2,025 | 4.5 | 6.3 | 224 | 54 | 125 | 200 | ..... | 2,141 |
| 4/13 | 110 | 2,050 | 4.1 | 3.0 | ... | 50 | 125 | 100 | ..... | 1,725 |
| 4/14 | 110 | 2,515 | 4.6 | .... | 156 | 50 | 125 | 100 | ..... | 1,725 |
| 4/15 | 110 | 1,985 | 5.0 | .... | ... | 50 | 125 | 100 | ..... | 1,725 |
| 4/16 | 110 | 1,645 | 4.5 | .... | ... | 52 | 140 | 126 | 26 Added | 1,972 |
| 4/17 | 110 | 1,735 | 5.0 | 2.2 | ... | 52 | 140 | 126 | 26 Added | 1,972 |
| 4/18 | 110 | 2,035 | 4.4 | .... | ... | 52 | 140 | 126 | 26 Added | 1,972 |
| 4/19 | 110 | 2,300 | 6.2 | Trace | 138 | 52 | 140 | 126 | 26 Added | 1,972 |
| 4/20 | 110 | 1,855 | 5.2 | Trace | ... | 52 | 140 | 126 | 26 Added | 1,972 |
| 4/21 | 109 | 2,370 | 4.9 | .... | ... | 52 | 140 | 126 | ..... | 1,972 |
| 4/22 | 110 | 2,125 | 6.1 | .... | ... | 52 | 140 | 126 | ..... | 1,972 |
| 4/23 | 109 | 1,915 | 4.7 | .... | ... | 52 | 140 | 126 | ..... | 1,972 |
| 4/24 | 110 | 1,625 | 4.5 | .... | ... | 52 | 140 | 126 | ..... | 1,972 |

* Diacetic acid present in urine (tests were made daily).
† Acetone present in urine (tests were made daily).

she had lost 10 pounds (4.5 Kg.). She was hungry and thirsty all of the time and had polyuria to such a degree that it was necessary for her to urinate four or five times each night. She complained that the skin of the face and lips seemed dry and the mouth parched. She was admitted to the hospital for study on Feb. 22, 1930. Complete data concerning the diet and laboratory observations made during the period of hospitalization and experimental study are given in table 4.

CASE 3.—C. J., a woman, aged 49, weighing 152 pounds (68.9 Kg.), had had influenza during the winter of 1929 from which convalescence was slow. Soon afterward an abscess developed in the soft tissue at the base of the spine. The attending physician examined the urine and discovered that sugar was present. The patient was then placed on a diet restricted in carbohydrates, without insulin. In December, she came under our care and was hospitalized on Jan. 8, 1930. Examination of the blood on that day showed 196 mg. of sugar; on January 13, 242 mg.; on January 22, 192 mg.; on January 28, 164 mg., and on February 3, 164 mg. per hundred cubic centimeters. During this time the diet was being regulated so that a fairly constant amount of urinary sugar would be excreted before the feeding with artichokes began. Data relative to the dietary regimen and laboratory observations are given in table 5.

## COMMENT

In this group of patients, after a fairly constant level of sugar excretion was obtained, the Jerusalem artichokes were included in the diet (1) by substitution for other carbohydrates to determine whether or not the carbohydrates of the artichoke would be better metabolized in the diabetic organism and (2) by addition to the diet as a further means of testing whether or not the artichoke contained some principle similar to the glucokinin of Collip,[14] which would stimulate better combustion of the carbohydrate fed.

In G. W. (table 3), there was no appreciable change in the diabetic condition, even when as much as 100 Gm. of artichoke carbohydrate, equivalent to 25 per cent of the total carbohydrate, was substituted. When as little as 20 Gm. of the artichoke carbohydrate was given in addition to the other carbohydrate, the patient excreted larger amounts of sugar than at any time previously, and the blood sugar rose sharply. Vain efforts were made to bring this patient back to his former condition both by omitting the added carbohydrate and by substituting artichokes in the diet; not until a marked decrease in the intake of carbohydrates was made, however, did the urine become free from sugar, and the blood sugar return to normal. We cannot account for the marked decrease in tolerance, which resulted when 20 Gm. of artichoke carbohydrate was added to the diet of this patient, and which necessitated a marked reduction in the intake of carbohydrate before

14. Collip, J. B.: Glucokinin: A New Hormone Present in Plant Tissue: Preliminary Paper, J. Biol. Chem. **56**:513, 1923; Glucokinin, J. Biol. Chem. **57**: 65, 1923.

TABLE 5.—*Data Concerning the Diet and Laboratory Observations in C. J.*

| | | Urine | | | | Diet | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Carbohydrate | | |
| Date, 1930 | Weight, Pounds | Volume, Cc. | Nitrogen, Gm. | Sugar, Gm. | Blood Sugar, Mg. | Protein, Gm. | Fat, Gm. | Total, Gm. | Artichoke, Gm. | Calories |
| 2/ 8 | 152 | 2,740 | 6.9 | 8.9 | ... | 50 | 140 | 200 | ..... | 2,260 |
| 2/ 9 | 152 | 3,375 | 8.3 | 7.8 | ... | 50 | 140 | 200 | ..... | 2,260 |
| 2/10 | 152 | 3,135 | 7.4 | 5.9 | ... | 50 | 140 | 200 | ..... | 2,260 |
| 2/11 | 152 | 2,535 | 6.9 | 11.2 | 168 | 50 | 140 | 200 | ..... | 2,260 |
| 2/12 | 152 | 2,550 | 6.0 | 7.8 | ... | 50 | 140 | 200 | 20 Subst. | 2,260 |
| 2/13 | 152 | 2,975 | 7.0 | 7.9 | ... | 50 | 140 | 200 | 20 Subst. | 2,260 |
| 2/14 | 153 | 2,290 | 7.2 | 10.8 | ... | 50 | 140 | 200 | 20 Subst. | 2,260 |
| 2/15 | 153 | 2,605 | 6.3 | 4.9 | ... | 50 | 140 | 200 | 20 Subst. | 2,260 |
| 2/16 | 152 | 3,145 | 6.4 | 10.6 | ... | 50 | 140 | 200 | 20 Subst. | 2,260 |
| 2/17 | 152 | 2,185 | 5.5 | 8.0 | ... | 50 | 140 | 200 | 20 Subst. | 2,260 |
| 2/18 | 153 | 3,115 | 8.1 | 6.9 | ... | 50 | 140 | 200 | 20 Subst. | 2,260 |
| 2/19 | 152 | 2,505 | 6.1 | 7.3 | 160 | 50 | 140 | 200 | 40 Subst. | 2,260 |
| 2/20 | 153 | 2,355 | 5.7 | 8.6 | ... | 50 | 140 | 200 | 40 Subst. | 2,260 |
| 2/21 | 154 | 2,430 | 5.1 | 5.6 | ... | 50 | 140 | 200 | 40 Subst. | 2,260 |
| 2/22 | 152 | 2,400 | 5.6 | 3.9 | ... | 50 | 140 | 200 | 40 Subst. | 2,260 |
| 2/23 | 154 | 2,250 | 6.5 | 12.2 | ... | 50 | 140 | 200 | 70 Subst. | 2,260 |
| 2/24 | 153 | 1,755 | 6.0 | 8.5 | ... | 50 | 140 | 200 | 70 Subst. | 2,260 |
| 2/25 | 155 | 2,385 | 6.4 | 6.6 | 134 | 50 | 140 | 200 | 70 Subst. | 2,260 |
| 2/26 | 154 | 2,490 | 6.8 | 10.1 | ... | 50 | 140 | 200 | 70 Subst. | 2,260 |
| 2/27 | 155 | 2,200 | 5.6 | 4.5 | ... | 50 | 140 | 200 | 100 Subst. | 2,260 |
| 2/28 | 155 | 1,965 | 6.2 | 4.2 | ... | 50 | 140 | 200 | 100 Subst. | 2,260 |
| 3/ 1 | 155 | 1,475 | 4.8 | 4.6 | ... | 50 | 140 | 200 | 100 Subst. | 2,260 |
| 3/ 2 | 156 | 1,815 | 5.5 | 2.4 | ... | 50 | 140 | 200 | 100 Subst. | 2,260 |
| 3/ 3 | 155 | 2,500 | 4.5 | 3.8 | 154 | 50 | 140 | 200 | 100 Subst. | 2,260 |
| 3/ 4 | 155 | 2,515 | 5.8 | 13.3 | ... | 50 | 140 | 200 | ..... | 2,260 |
| 3/ 5 | 155 | 1,575 | 5.3 | 17.3 | ... | 50 | 140 | 200 | ..... | 2,260 |
| 3/ 6 | 153 | 3,065 | 6.8 | 20.4 | ... | 50 | 140 | 200 | ..... | 2,260 |
| 3/ 7 | 154 | 1,965 | 6.6 | 26.2 | ... | 50 | 140 | 200 | ..... | 2,260 |
| 3/ 8 | 154 | 2,405 | 6.8 | 31.0 | ... | 50 | 140 | 220 | 20 Added | 2,340 |
| 3/ 9 | 155 | 2,435 | 7.1 | 16.4 | ... | 50 | 140 | 220 | 20 Added | 2,340 |
| 3/10 | 154 | 2,135 | 7.7 | 11.2 | ... | 50 | 140 | 220 | 20 Added | 2,340 |
| 3/11 | 155 | 2,070 | 6.8 | 9.7 | 172 | 50 | 140 | 220 | 20 Added | 2,340 |
| 3/12 | 154 | 2,565 | 6.7 | 10.4 | ... | 50 | 140 | 220 | 20 Added | 2,340 |
| 3/13 | 155 | 1,725 | 5.6 | 9.6 | 144 | 50 | 140 | 220 | 20 Added | 2,340 |
| 3/14 | 155 | 2,240 | 7.0 | 20.1 | ... | 50 | 140 | 220 | 20 Added | 2,340 |
| 3/15 | 155 | 2,200 | 4.9 | 16.3 | 170 | 50 | 140 | 220 | 20 Added | 2,340 |
| 3/16 | 155 | 2,040 | 5.8 | 13.3 | ... | 50 | 140 | 220 | 20 Added | 2,340 |
| 3/17 | 155 | 1,810 | 7.0 | 6.2 | 168 | 50 | 140 | 220 | ..... | 2,340 |
| 3/18 | 155 | 1,980 | .... | 13.4 | ... | 50 | 140 | 220 | ..... | 2,340 |
| 3/19 | 155 | 2,820 | 7.3 | 14.1 | 196 | 50 | 140 | 220 | ..... | 2,340 |
| 3/20 | 156 | 2,630 | 6.2 | 16.7 | ... | 50 | 140 | 220 | ..... | 2,340 |
| 3/21 | 156 | 1,960 | 6.8 | 17.7 | 174 | 50 | 140 | 220 | ..... | 2,340 |
| 3/22 | 156 | 1,865 | 6.6 | 19.3 | ... | 50 | 140 | 220 | ..... | 2,340 |
| 3/23 | 156 | 2,490 | 6.8 | 26.4 | ... | 50 | 140 | 220 | ..... | 2,340 |
| 3/24 | 154 | 1,900 | 8.5 | 31.0 | 188 | 50 | 140 | 220 | ..... | 2,340 |
| 3/25 | 156 | 1,560 | 7.9 | 25.0 | ... | 50 | 140 | 220 | ..... | 2,340 |
| 3/26 | 157 | 1,940 | 7.6 | 26.7 | 202 | 50 | 140 | 200 | ..... | 2,260 |
| 3/27 | 156 | 2,180 | 8.4 | 29.3 | ... | 50 | 140 | 200 | ..... | 2,260 |
| 3/28 | 157 | 1,760 | 6.0 | 13.1 | 190 | 50 | 140 | 200 | ..... | 2,260 |
| 3/29 | 157 | 2,230 | 6.7 | 25.5 | ... | 50 | 140 | 200 | ..... | 2,260 |
| 3/30 | 157 | 1,425 | 6.3 | 32.0 | ... | 50 | 140 | 200 | ..... | 2,260 |
| 3/31 | 156 | 1,140 | 4.9 | 9.1 | 180 | 50 | 140 | 200 | 100 Subst. | 2,260 |
| 4/ 1 | 158 | 2,340 | 8.6 | 30.7 | ... | 50 | 140 | 200 | 100 Subst. | 2,260 |
| 4/ 2 | 159 | 1,500 | 6.1 | 11.0 | 200 | 50 | 140 | 200 | 100 Subst. | 2,260 |
| 4/ 3 | 159 | 1,500 | 4.6 | 15.0 | ... | 50 | 140 | 200 | 100 Subst. | 2,260 |
| 4/ 4 | 159 | 2,260 | 5.9 | 32.1 | 196 | 50 | 140 | 150 | ..... | 2,060 |
| 4/ 5 | 158 | 2,380 | 6.8 | 48.9 | ... | 50 | 140 | 150 | ..... | 2,060 |
| 4/ 6 | 158 | 2,580 | 7.9 | 50.6 | ... | 50 | 140 | 150 | ..... | 2,060 |
| 4/ 7 | 158 | 1,970 | 8.4 | 55.7 | ... | 50 | 140 | 150 | ..... | 2,060 |
| 4/ 8 | 157 | 2,850 | 7.2 | 20.9 | 192 | 50 | 140 | 150 | ..... | 2,060 |
| 4/ 9 | 158 | 2,570 | 4.0 | 7.8 | ... | 50 | 140 | 150 | ..... | 2,060 |
| 4/10 | 157 | 2,045 | 7.0 | 28.2 | 182 | 50 | 100 | 150 | ..... | 1,700 |
| 4/11 | 157 | 2,260 | 8.4 | 50.5 | ... | 50 | 100 | 150 | ..... | 1,700 |
| 4/12 | 157 | 1,930 | 5.6 | 37.3 | 188 | 50 | 100 | 150 | ..... | 1,700 |
| 4/13 | 157 | 2,405 | 9.1 | 44.3 | ... | 60 | 100 | 100 | ..... | 1,540 |
| 4/14 | 157 | 1,740 | 7.6 | 34.4 | 216 | 60 | 100 | 100 | ..... | 1,540 |
| 4/15 | 157 | 2,285 | 9.1 | 23.6 | ... | 60 | 100 | 100 | ..... | 1,540 |
| 4/16 | 157 | 1,780 | 7.6 | 39.3 | ... | 60 | 100 | 100 | ..... | 1,540 |
| 4/17 | 157 | 1,985 | 8.5 | 19.2 | ... | 60 | 100 | 100 | ..... | 1,540 |
| 4/18 | 157 | 2,395 | 7.1 | 12.2 | ... | 60 | 100 | 50 | ..... | 1,340 |
| 4/19 | 157 | 2,085 | .... | 24.8 | 186 | 60 | 100 | 50 | ..... | 1,340 |
| 4/20 | 157 | 2,420 | 8.6 | 15.0 | ... | 60 | 100 | 50 | ..... | 1,340 |
| 4/21 | 157 | 2,200 | 11.0 | 10.1 | ... | 60 | 100 | 50 | ..... | 1,340 |
| 4/22 | 158 | 1,575 | 7.6 | 5.0 | ... | 60 | 100 | 50 | ..... | 1,340 |
| 4/23 | 158 | 1,625 | 6.5 | 5.4 | ... | 60 | 100 | 50 | ..... | 1,340 |
| 4/24 | 156 | 1,695 | 9.8 | 7.8 | ... | 60 | 100 | 50 | ..... | 1,340 |
| 4/25 | 156 | 2,280 | 10.3 | 13.7 | 154 | 60 | 100 | 50 | ..... | 1,340 |

the diabetic condition, as judged by the excretion of urinary sugar and by blood sugar, became as satisfactory as it was previous to the feeding of the artichokes. This upset may have been, and probably was, merely coincidental to the artichoke regimen, although the long continued strain on the pancreas resulting from the high carbohydrate diet may in itself be sufficient to account for it.

In A. R. (table 4), no change in the excretion of dextrose prevailed when artichoke carbohydrate was substituted in the diet. On the other hand, when artichokes were added to the diet, the urine became sugar-free and remained so, even when the addition of artichoke carbohydrate reached 100 Gm. The conclusion that artichokes in the diet of the diabetic patient have a beneficial effect might easily be drawn from this latter observation. If we had stopped our study at this point, we should have been forced to make such an interpretation of our results. However, in this case an examination of our data shows that such an assumption would be unwarranted; for, when the artichokes were omitted from the diet and were replaced by 100 Gm. of other carbohydrate, there was still no glycosuria, showing that the tolerance for dextrose had increased during this period. In fact, the urine was sugar-free even after the diet had reached 200 Gm. of carbohydrate, 50 Gm. of protein and 150 Gm. of fat. The enthusiastic reports that we have received from physicians concerning the therapeutic value of artichokes in diabetes are probably based on experiences similar to this one of ours, in which artichokes were used before the patient's tolerance to carbohydrate had been established. Our experience with this patient offers a striking example of how erroneous such conclusions may be. Further studies on this patient, after the tolerance had been established, gave no evidence that the artichokes had therapeutic value. When artichoke carbohydrate was added to the diet of higher carbohydrate content, both the urinary sugar and the blood sugar increased. The urine again became sugar-free when the diet was reduced to 100 Gm. of carbohydrate, 50 Gm. of protein and 125 Gm. of fat, which was enough to satisfy the patient's appetite and make her comfortable, as she had had intense abdominal distress during the period of heavier feeding. When 25 Gm. of flakes (13 Gm. of artichoke carbohydrate) was given at 10 a. m. and 3 p. m., respectively, she again complained of the severe formation of gas, and sugar appeared in the urine, but disappeared when the artichokes were omitted. Thus, this case offers no support to the claims that the carbohydrate of the artichoke is better utilized by the diabetic patient than that of other sources.

In patient C. J. (table 5), there was little change in the glycosuria until the last few days of the first period of substitution when 100 Gm. of artichoke carbohydrate was fed. Then there was a slight reduction in

the amount of sugar excreted. During the subsequent four day period in which there were no artichokes in the diet, there was a marked average increase in the glycosuria. Later, when artichoke carbohydrate was added to the diet, a decrease in the urinary sugar again occurred, even though the intake of carbohydrate had been increased. On substituting an equivalent amount of other carbohydrate for that contained in the added artichoke, there resulted a moderate average increase in the excretion of dextrose, which continued even after the extra carbohydrate had been omitted and the intake of carbohydrate had been returned thereby to its former level. When 100 Gm. of artichoke carbohydrate was again substituted in this diet, the excretion of dextrose decreased somewhat. After the removal of the artichokes from the diet, there was an increase in the amount of sugar elimination, in spite of the fact that the intake of carbohydrate was at the same time decreased. Thus, it is apparent that there has been a lowered excretion of sugar in each period of the feeding of artichokes, with a subsequent increase in the output of dextrose when the artichokes have been withdrawn. We feel that it would be entirely unwarranted to claim without reservation that this was the result of greater tolerance to the carbohydrate of the artichoke, or to some beneficial effect of the artichoke whereby the carbohydrate is better metabolized. Throughout the entire time that the artichokes were fed, this patient complained of abdominal distress, which was undoubtedly due to excessive fermentation, an occurrence that is rather common when the artichokes are first eaten, as has already been mentioned. This would result in a decrease of the assimilable carbohydrate sufficient to account for the fall in the amount of urinary dextrose which was found when artichokes were fed. That there has been no real increase of tolerance to carbohydrate in this patient is further supported by the fact that an increase in blood sugar followed the addition of artichokes to the diet and continued until the intake of carbohydrate was markedly decreased in the latter part of the experimental period. At the end of the experimental period, it was necessary to reduce the intake of carbohydrate much below that given earlier before the elimination of sugar could be reduced to the same low level that originally prevailed. To say that this decreased tolerance was due to the previous feeding of artichokes would be just as unwarranted as to claim that the artichokes had a beneficial effect when they were first fed. The only fair interpretation to make of our data in this case is that the artichoke proved of no value other than to provide variety to the diet.

Thus, if our interpretation of results is correct, the carbohydrate of the artichoke was not utilized any better by our patients than was carbohydrate from other sources, and no evidence was obtained to

indicate that the artichokes contained any insulin-like constituent that would promote the metabolism of carbohydrate.

Our results do not conflict with the observations of Root and Baker [6] and of Carpenter and Root [7] concerning the utilization and metabolism of carbohydrates from Jerusalem artichokes. To be sure, we did not make an examination of the feces for unabsorbed carbohydrate or study the respiratory exchange to determine the comparative metabolism of carbohydrate during the periods of artichoke feeding. However, the fact that there was no marked reduction in the excretion of sugar when 100 Gm. of artichoke carbohydrate was substituted in the diet indicates definitely that a large part of the carbohydrates was absorbed and utilized by our patients.

Our data show that Jerusalem artichokes may be eaten in moderation by patients with diabetes mellitus without causing an increase in the excretion of dextrose when glycosuria is present. We feel justified in the further assumption, based on *a priori* reasoning, that moderate amounts of artichokes may be eaten without producing glycosuria in patients in whom the urine has remained sugar-free. Furthermore, our inquiries have elicited the information that permission to eat Jerusalem artichokes is welcomed and appreciated by patients with diabetes mellitus for the reason that the additional vegetable provides greater variety to the necessarily limited diet of the diabetic person.

## CONCLUSIONS

1. The carbohydrates of the Jerusalem artichoke are absorbed and utilized by patients with diabetes mellitus of the mild to moderate type, but they are no better tolerated than carbohydrates from other sources.

2. Whenever we have obtained an apparent beneficial effect from feeding artichokes, there has also occurred a formation of large amounts of intestinal gas arising from bacterial fermentation. Consequently, there must have been a simultaneous reduction in the amount of assimilable carbohydrate sufficient to account for the decrease in the amount of sugar eliminated.

3. We believe that the reputed therapeutic value of Jerusalem artichokes in the diet of the diabetic patient, reported frequently by physicians from their personal experience, is based too often on uncontrolled observations, and is a result both of overenthusiasm on the part of the observer and of the tendency of human nature to anticipate results, even at the expense of erroneous conclusions.

4. As moderate amounts of Jerusalem artichokes may be given without harm to patients with diabetes mellitus, physicians may well adopt the practice of using this vegetable to furnish variety to their prescribed diabetic diets.

# EFFECTS OF TREATMENT WITH OXYGEN IN CARDIAC FAILURE*

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A state of deficiency of oxygen in the blood, or anoxemia, may be produced by diminishing the concentration of oxygen in the air breathed, or, as is usual in clinical disease, through an impairment of the functional activity of the respiratory or circulatory system. An adequate transportation of oxygen from the lungs to the tissues is maintained by the normal heart. In cardiac disease an impairment of this function exists, although the significance of this type of anoxemia in the symptomatology of cardiac failure is not clearly understood.

## HISTORICAL SURVEY

Various aspects of the factor of the deficiency of oxygen in the blood in the production of the symptoms of cardiac failure have been under investigation for the past two decades. In 1915, Means and Newburgh [1] found a diminished oxygen saturation in the venous blood in cases of cardiac insufficiency. Their results were confirmed in a larger number of cases by Lundsgaard.[2] Of considerable interest was Harrop's discovery [3] in 1919 that the oxygen saturation of arterial blood was also diminished in cardiac decompensation. These obser-

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* From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital.

* Part of the expenses of this study were defrayed by the Linde Air Products Company.

* A preliminary report of this investigation appeared in the Proceedings of the Society for Experimental Biology and Medicine (**27**:308 [Jan.] 1930).

1. Means, J. H., and Newburgh, L. H.: Studies of the Blood Flow by the Method of Krogh and Lindhard, Tr. A. Am. Physicians **30**:51, 1915.

2. Lundsgaard, C.: Studies of Oxygen in the Venous Blood: II. Oxygen Unsaturation in the Venous Blood of a Group of Patients with Circulatory Disturbances, J. Exper. Med. **27**:179, 1918.

3. Harrop, G. A.: The Oxygen and Carbon Dioxide Content of Arterial and of Venous Blood in Normal Individuals and in Patients with Anemia and Heart Disease, J. Exper. Med. **30**:241, 1919.

vations were later confirmed by Barach and Woodwell,[4] and by Campbell, Hunt and Poulton.[5]

In 1913, Lewis, Ryffel, Wolf, Cotton and Barcroft,[6] by using the value K of Hill's equation, reached the conclusion that an increase in the fixed acid of the blood occurred in decompensation of the heart. These observations have been extended by Meakins and Long [7] who found an actual increase in the lactic acid of the blood.

The position of the carbon dioxide dissociation curve in cases of cardiac insufficiency is modified by emphysema, renal disease and other conditions, but most investigation has shown that it is either normal or lowered. Beddard and Pembrey [8] observed a reduction in the alveolar carbon dioxide in cardiac decompensation. Fitzgerald,[9] and later Porges, Leimdörfer and Marcovici,[10] showed that the alveolar carbon dioxide was low in patients having cardiac disease with dyspnea and normal in those without dyspnea. Peabody [11] found that the lowered alveolar carbon dioxide during the period of decompensation was followed by a rise when compensation was restored.

The relation between the alveolar and the arterial carbon dioxide tensions was studied by Peters and Barr,[12] who found that the alveolar values were decidedly lower than the arterial in cases of advanced decompensation. The same observation was noted by Campbell and

4. Barach, A. L., and Woodwell, M. N.: Studies in Oxygen Therapy with Determination of Blood Gases: I. In Cardiac Insufficiency and Related Conditions, Arch. Int. Med. **28**:367 (Oct.) 1921.

5. Campbell, J. M. H.; Hunt, G. H., and Poulton, E. P.: An Examination of the Blood Gases and Respiration in Disease, J. Path. & Bact. **26**:234, 1923.

6. Lewis, T.; Ryffel, J. H.; Wolf, C. G. L.; Cotton, T., and Barcroft, J.: Observations Relating to Dyspnea in Cardiac and Renal Patients, Heart **5**:45, 1913.

7. Meakins, J., and Long, C. N. H.: Oxygen Consumption, Oxygen Debt, and Lactic Acid in Circulatory Failure, J. Clin. Investigation **4**:273, 1927.

8. Beddard, A. P., and Pembrey, M. S.: Observations on Pulmonary Ventilation in Disease, Brit. M. J. **2**:580, 1908.

9. Fitzgerald, M. P.: The Alveolar Carbonic Acid Pressure in Diseases of the Blood and in Diseases of the Respiratory and Circulatory Systems, J. Path. & Bact. **14**:328, 1909-1910.

10. Porges, O.; Leimdörfer, A., and Marcovici, E.: Ueber die Kohlensäuerspannung des Blutes in pathologischen Zuständen, Ztschr. f. klin. Med. **77**:446, 1913.

11. Peabody, F. W.: Studies on Acidosis and Dyspnea in Renal and Cardiac Disease, Arch. Int. Med. **14**:236 (Aug.) 1914.

12. Peters, J. P., Jr., and Barr, D. P.: Carbon Dioxide Curve and Carbon Dioxide Tension of Blood in Cardiac Dyspnea, J. Biol. Chem. **45**:537, 1921.

Poulton,[13] DAutrebande, Fetter and Meakins [14] later showed that the use of arterial rather than venous blood for the construction of the carbon dioxide curves reduced this discrepancy to a great extent in cases of moderate decompensation.

The carbon dioxide dissociation curves of the blood were found by Peters and Barr [12] to be at normal levels in mild or moderate cases of cardiac insufficiency, but definitely reduced in certain cases of advanced cardiac failure, particularly those with marked cyanosis.

The hydrogen ion concentration of the arterial blood in cardiac disease may be altered by associated pulmonary or renal disease, by the administration of morphine and by other complicating factors. In general, it has been reported to be within normal limits in mild or moderate degrees of cardiac failure and to be definitely acid in extreme failure, with return to normal when compensation was restored (Peters and Barr [12]). Instances of an alkaline $p_H$ in a few cases of cardiac dyspnea have been reported by Meakins,[14] and by Campbell, Hunt and Poulton.[5] Fraser, Ross and Dreyer [15] reported nine cases of alkalemia in patients with severe cardiac failure; their method of determining the $p_H$, however, was the Dale-Evans dialysis technic, and, as no account was taken of the Donnan effect, the accuracy of their results may be questioned.

In 1908, Beddard and Pembrey [8] observed that the inhalation of oxygen resulted in decreased pulmonary ventilation in a patient with cardiac insufficiency. This observation was later reported by Campbell and Poulton,[16] who also observed a corresponding increase in the carbon dioxide concentration of the expired air. It is interesting to note that in normal animals living in an atmosphere containing a high degree of oxygen, J. A. Campbell [17] noted an increase in the tissue tensions of both oxygen and carbon dioxide.

In 1921, Barach and Woodwell [4] studied the effects of the inhalation of from 40 to 60 per cent oxygen mixtures over periods of from two to four hours in patients with cardiac insufficiency. They found that the arterial anoxemia was relieved, the oxygen saturation of

13. Campbell, J. M. H., and Poulton, E. P.: The Relation of Oxygen Hemoglobin to the $CO_2$ of the Blood, J. Physiol. **54**:152 and 166, 1920-1921.

14. DAutrebande, L.; Fetter, W. J., and Meakins, J. C.: Influence of Circulatory Disturbances on Gaseous Exchange of Blood; Blood Gases and Circulation Rate in Cases of Mitral Stenosis, Heart **10**:153, 1923.

15. Fraser, F. R.; Ross, J. P., and Dreyer, N. B.: Reaction of Blood in Relation to Dyspnoea, Quart. J. Med. **15**:195, 1922.

16. Campbell, J. M. H., and Poulton, E. P.: The Effect on Breathless Subjects of Residence in an Oxygen Chamber, Quart. J. Med. **20**:141, 1926-1927.

17. Campbell, J. A.: Prolonged Alterations of Oxygen Pressure in the Inspired Air with Special Reference to Tissue Oxygen Tension, Tissue Carbon Dioxide Tension and Haemoglobin, J. Physiol. **62**:211, 1927.

arterial blood being elevated to, or near, the normal level. An increase in the oxygen saturation of venous blood also occurred, apparently proportional to the change in that of arterial blood. The outstanding, objective, clinical results were a diminution of the cyanosis and a slowing of the pulse rate. In some cases a distinct increase in the carbon dioxide content of the arterial and venous blood took place. In two instances of right bundle branch block, a decreased notching and a diminished height of the R wave were present during the inhalation of oxygen.

Recently, Baker [18] reported a case of bundle branch block in which the inhalation of oxygen resulted in a disappearance of the aberrant ventricular complexes and a striking improvement in intraventricular conductivity.

In most of the previous studies the obvious difficulty in determining the effect of oxygen therapy in cardiac disease has been a technical one, in that it was not possible to keep patients continuously in atmospheres containing a high degree of oxygen over considerable periods of time. This hindrance has been overcome by the use of an oxygen chamber in which the patient may reside in an atmosphere containing 45 per cent oxygen in comfort for weeks or months at a time.

## METHODS

In the present investigation, throughout which the Barach oxygen chamber was used, we studied eight patients who were suffering from various forms of circulatory failure.

The method of study varied considerably in detail according to the clinical situation. The general plan was as follows: The patient was first given the benefit of treatment in the ward for a number of days (see clinical histories), with digitalis and other treatment as indicated. At a time when his condition either appeared to be stationary or was becoming worse, he was transferred to the oxygen room. In certain cases an additional control period was carried out in the oxygen room, in which the temperature was maintained at 66 degrees, the relative humidity at 40 per cent and the oxygen concentration at 21 per cent. The concentration of oxygen in the chamber was then raised to 45 per cent, and the patient was kept in this atmosphere for from three to sixty days.

After a number of days in an atmosphere containing a high degree of oxygen, and when, clinically, the patient's condition seemed to be changing little from one day to the next, the concentration was lowered to 21 per cent and maintained at this level for three or four days, with the patient remaining in the chamber. This was done expressly to rule out the possibility that the changes that were observed in the patient's condition during residence in the oxygen chamber were simply due to the alteration in temperature and humidity from those in the ward. Usually he was given a high amount of oxygen for a further period, after which the concentration was lowered gradually over a day or two; the patient was then returned to the ward. Sometimes it was necessary to give the patient further treatment with oxygen by nasal catheter.

18. Baker, B. M.: The Effect of Cardiac Rate and the Inhalation of Oxygen on Transient Bundle Branch Block, Arch. Int. Med. **45**:814 (May) 1930.

The Barach oxygen chamber has been described elsewhere.[19] The ventilation is by thermal circulation of the air. The temperature can generally be kept constant within 2 degrees; in this investigation for most of the time it was between 64 and 66 degrees; the humidity was regulated between 35 and 40 per cent. The oxygen concentration was maintained at 45 per cent, with a range of 2 or 3 per cent. The carbon dioxide concentration varied between 0.15 and 0.5 per cent.

All of the patients (except I. S., case 8) were given a measured intake of fluids and a "cardiac diet" (limited amount of fluids, low in salt, with small, frequent feedings), and their output of urine was measured. The administration of digitalis, sedatives and other treatment was kept, as far as possible, the same when the patient was in an atmosphere containing a high degree of oxygen as during the control periods. No diuretics were given at any time during the period of observation.

Determinations of the basal metabolic rate were made with the Benedict-Roth apparatus. Ventilation was calculated from the graphic records of the respiration obtained with this apparatus, except in cases 3 (J. Sn.), 7 (A. S.) and 8 (I. S.), in which the expired air was collected in a Douglas bag.

Studies of the blood were made on arterial samples that were drawn in the morning under basal conditions from the brachial (occasionally the radial) artery. For determinations of the oxygen and carbon dioxide, blood was transferred under oil to containers with small amounts of dried neutral potassium oxalate and sodium fluoride. In the construction of carbon dioxide curves of oxygenated whole blood, sometimes two points were determined, sometimes only one, in which latter case the slope was estimated from the oxygen capacity (see Peters, Bulger and Eisenman,[20] and Richards and Strauss[21]). The Van Slyke-Neill manometric apparatus was used for measurements of gas in the blood, and the Boothby modification of the Haldane apparatus for the analyses of gas. A correction was made in the carbon dioxide values of the blood after equilibration in the tonometers, owing to loss of carbon dioxide capacity during this procedure.[22] Arterial $p_H$ values were calculated from the carbon dioxide content of arterial whole blood and from the carbon dioxide curves, the graphic method described by Van Slyke and Sendroy[23] being used. In the determination of the cardiac output in cases 6 (J. Sr.), 7 (A. S.), 3 (J. Sn.) and 8 (I. S.), the Fick principle was employed with carbon dioxide from arterial blood as measured, and the carbon dioxide content of mixed venous blood obtained by a technic previously described by Richards and Strauss.[21] The output of carbon dioxide was found by collecting expired air in a Douglas bag and analyzing for carbon dioxide.

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19. Barach, A. L.: A New Type of Oxygen Chamber, J. Clin. Investigation **2**:463 (Aug. 20) 1926; New Oxygen Chamber Ventilated by Thermal Circulation of Air, Mod. Hosp. **32**:144 (Jan.) 1929.

20. Peters, J. P.; Bulger, H. A., and Eisenman, A. J.: Studies of Carbon Dioxide Absorption: IV. J. Biol. Chem. **58**:747, 1923.

21. Richards, D. W., and Strauss, M. L.: Circulatory Adjustment in Anemia, J. Clin. Investigation **5**:161, 1928.

22. Bock, A. V.; Dill, D. B.; Edwards, H. T.; Henderson, L. J., and Talbott, J. H.: On Partial Pressures of Oxygen and Carbon Dioxide in Arterial Blood and Alveolar Air, J. Physiol. **68**:277, 1929.

23. Van Slyke, D. P., and Sendroy, J., Jr.: Studies of Gas and Electrolyte Equilibria in Blood: Line Charts for Graphic Calculation by Henderson-Hasselbalch Equation and for Calculation of Plasma Carbon Dioxide Content from Whole Blood Content, J. Biol. Chem. **79**:781, 1928.

RESULTS

Of the eight cases studied, six were primarily of cardiac disease, the remaining two primarily of pulmonary disease with secondary circulatory failure. The effects on these patients of continuous residence in atmospheres containing a high degree of oxygen are shown in the clinical histories and in the accompanying tables and charts.

It will be noted that the most consistent and pronounced effects were obtained in the following three patients, all of whom had marked congestive cardiac failure: case 1, A. L., a 55 year old Negress, with cardiac insufficiency based on myocardial fibrosis and general arteriosclerosis; case 2, J. McQ., a man of 53 years, with cardiac insufficiency, together with a large aortic aneurysm, and case 3, J. Sn., a man of 30 years, with cardiac insufficiency associated with advanced fibrosis of the lung.

In these patients the major effects of the inhalation of an atmosphere containing 45 per cent oxygen were: 1. There were marked subjective improvement, decrease of cyanosis, relief of dyspnea, orthopnea and cough, beginning generally within three hours after the entrance of the patients into an atmosphere containing a high degree of oxygen. 2. There was an increase of urinary output and disappearance of edema of gradual onset which usually did not reach its maximum for from three to five days. In (case 3) J. Sn., the diuresis was paralleled by a marked loss in weight. In the other two cases the weight was not measured. In all three patients a return to an atmosphere containing a normal amount of oxygen resulted in a decreased urinary output and a return of edema. When the oxygen concentration was again raised a second diuresis was brought about. In cases 1 (A. L.) and 2 (J. McQ.) this sequence was obtained both by transferring the patient from the oxygen room to the ward, and by lowering and raising the oxygen in the chamber without removing the patient from it. In J. Sn., this course could not be followed, but at a later time the same result was obtained while the patient was in the ward; the administration of oxygen by nasal catheter was stopped, and it was then resumed after the patient had shown definite signs of the retention of water (decreased output and increased weight).

3. There was increased oxygen saturation of arterial blood. This was definite and marked for A. L. (case 1) and J. Sn. (case 3), as shown in the tables. In case 2 (J. McQ.), unfortunately, the earlier measurements of arterial oxygen were vitiated by the fact that a determination of the basal metabolic rate (a very high degree of oxygen being used for rebreathing) was performed just before the arterial puncture, and sufficient time was not allowed for the patient's arterial blood to return

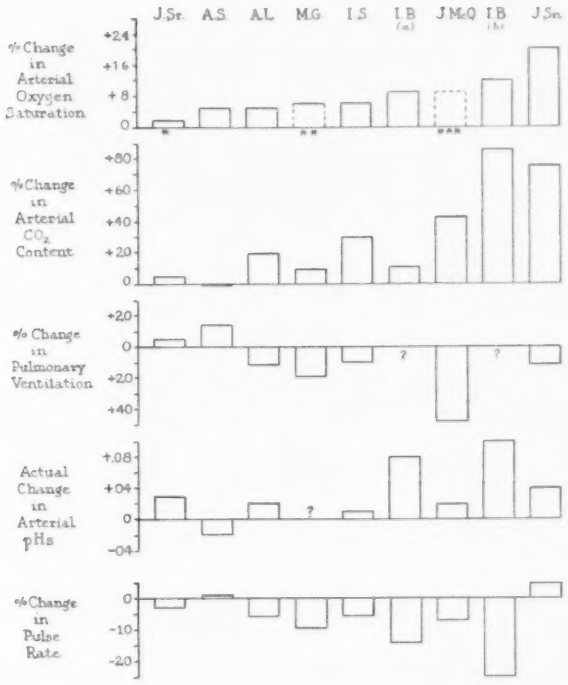


Chart 1.—Changes in the oxygen saturation of arterial blood, in the carbon dioxide content of arterial blood, in pulmonary ventilation, in arterial $p_H$ and in pulse rate, following the residence of the patients in an atmosphere containing a high degree (45 per cent) of oxygen. The initials represent the individual patients. Patient I. B. (case 5) was studied over two periods: (*a*) from September 27 to October 12, and (*b*) from October 15 to October 19. Table gives further details. * The oxygen saturation of arterial blood while the patient was residing in an atmosphere containing 45 per cent oxygen was not measured, but it was normal even when the atmosphere contained but 21 per cent oxygen. ** An estimate, based on the facts that (*a*) clinical cyanosis was always marked but not extreme, (*b*) little observable change occurred while the patient was in an atmosphere that contained 45 per cent oxygen and (*c*) the oxygen saturation of arterial blood under the conditions just mentioned was only 87 per cent. *** An estimate, based on the facts that (*a*) oxygen saturation of arterial blood while the patient was in the ward, in a state of decompensation, was 84 per cent, and that (*b*) clinically, cyanosis cleared completely while he was in an atmosphere that contained 45 per cent oxygen.

TABLE 1.—*Circulatory and Respiratory Changes with Varying Oxygen Concentrations of Respired Air* *

| Case | Date | Per Cent of Oxygen in Atmosphere | Arterial Oxygen Content, per Cent by Volume | Arterial Oxygen Capacity, per Cent by Volume | Per Cent of Oxygen Saturation of Arterial Blood | Arterial Carbon Dioxide Content, per Cent by Volume | Arterial Carbon Dioxide Tension, Mm. | Carbon Dioxide of Arterial Blood at 40 Mm. | Arterial $p_H$ | Ventilation, Liters per Minute | Average Vital Capacity, Liters | Basal Metabolic Rate | Average Pulse Rate | Average Respiratory Rate | Average Temperature | Average Systolic Pressure | Average Diastolic Pressure | Cardiac Output of Liters per Minute |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A. L. | July 6 | 45 | 18.0 | 18.7 | 96 | 53.4 | 40.7 | 52.9 | 7.45 | 7.2 | ... | + 2 | 60 | 25 | 98.6 | 145 | 65 | ... |
| | 16 | 25 | 17.8 | 19.5 | 91 | 45.0 | 36.0 | 47.1 | 7.43 | 7.7 | 0.6 | + 5 | 66 | 24 | 98.6 | 131 | 69 | ... |
| J. McQ. | Aug. 16 | 21 | .... | 20.7 | .. | 40.9 | .... | .... | .... | 11.8 | 1.8 | +29 | 84 | 25 | 99.3 | 129 | 59 | ... |
| | 22 | 45 | .... | .... | .. | .... | .... | .... | .... | 7.5 | 2.4 | +17 | 76 | 15 | 98.6 | 115 | 54 | ... |
| | 30 | 45 | .... | 17.6 | .. | 38.3 | 41.0 | 57.7 | 7.48 | 6.2 | 2.2 | + 4 | 78 | 14 | 98.8 | 120 | 40 | ... |
| | Sept. 6 | 20 | .... | 16.5 | .. | 36.1 | 40.6 | 55.5 | 7.46 | 6.3 | 2.0 | + 8 | 85 | 17 | 99.2 | .... | .. | ... |
| | 25 | 35 | .... | .... | .. | 53.8 | .... | .... | .... | 6.2 | 2.2 | +10 | 72 | 19 | 99.2 | .... | .. | ... |
| | Oct. 5 | 21 | 14.5 | 17.4 | 83 | 50.3 | 36.2 | 51.7 | 7.47 | 6.6 | 2.2 | — 7 | 76 | 21 | 99.4 | 120 | 40 | ... |
| J. Sn.† | Dec. 23 | 21 | 17.1 | 24.2 | 71 | 35.4 | .... | .... | .... | .... | .... | .... | 108 | 25 | 101.4 | 105 | 87 | ... |
| | Jan. 2 | 45 | 16.2 | .... | .. | 69.9 | 50.0 | 64.2 | 7.48 | .... | 0.8 | .... | 116 | 22 | 101.0 | 120 | 81 | ... |
| | 6 | 45 | 16.5 | 18.4 | 90 | 67.3 | 50.6 | 61.5 | 7.44 | 10.3 | 0.8 | .... | 116 | 22 | 101.0 | 124 | 80 | 4.8 |
| | 19 | 25‡ | 17.8 | 19.0 | 94 | 56.8 | .... | .... | .... | .... | 1.4 | .... | 110 | 22 | 100.4 | 110 | 82 | ... |
| | 25 | 25‡ | 16.0 | 18.4 | 87 | 52.7 | .... | .... | .... | .... | 1.6 | .... | 106 | 21 | 99.6 | 114 | 90 | ... |
| | Mar. 6 | 25‡ | 16.9 | 19.7 | 86 | 48.9 | .... | .... | .... | .... | .... | .... | 106 | 21 | 99.8 | .... | .. | ... |
| | 27 | 21 | 11.7 | 18.0 | 65 | .... | .... | .... | .... | .... | 1.0 | .... | 116 | 24 | 100.4 | 112 | 70 | ... |
| M. G. | Sept. 29 | 21 | 16.9 | .... | .. | 44.6 | .... | .... | .... | 10.5 | 1.5 | +17 | 86 | 21 | 100.4 | .... | .. | ... |
| | Oct. 12 | 45 | 17.3 | 19.9 | 87 | 48.7 | 38.5 | 48.8 | 7.42 | 8.5 | 1.6 | + 6 | 80 | 24 | 99.8 | 185 | 85 | ... |
| I. B. | Sept. 27 | 21 | 19.3 | 23.0 | 84 | 37.2 | .... | .... | .... | .... | 1.3 | .... | 92 | 24 | 100.2 | 150 | 80 | ... |
| | Oct. 12 | 45 | 22.8 | 24.4 | 93 | 41.2 | 35.2 | 43.9 | 7.44 | .... | 1.2 | .... | 77 | 27 | 100.2 | .... | .. | ... |
| | 15 | 25‡ | 19.7 | 23.5 | 84 | 26.4 | 25.2 | 33.9 | 7.36 | .... | .... | .... | 106 | 35 | 101.4 | 90 | ? | ... |
| | 19 | 45 | 21.3 | 21.8 | 98 (?) | 49.0 | 38.0 | 50.9 | 7.46 | .... | .... | .... | 80 | 27 | 99.8 | 118 | 78 | ... |
| J. Sr. | July 23 | 21 | 18.3 | 20.4 | 91 | 44.0 | .... | .... | .... | 12.3 | 3.3 | + 9 | 74 | 24 | 98.8 | 106 | 77 | ... |
| | 29 | 21 | 20.9 | 21.6 | 97 | 46.2 | 32.0 | 50.5 | 7.50 | 9.3 | 3.3 | + 2 | 70 | 25 | 98.8 | 106 | 80 | 3.2 |
| | Aug. 6 | 21 | 20.0 | 21.0 | 95 | 43.4 | 34.0 | 46.9 | 7.45 | 11.4 | 3.0 | + 2 | 72 | 24 | 98.2 | 119 | 80 | ... |
| | 13 | 45 | 20.8 | .... | .. | 46.4 | 32.2 | 50.6 | 7.51 | 11.6 | 2.6 | +10 | 70 | 24 | 98.8 | 126 | 85 | 3.5 |
| | 23 | 21 | .... | .... | .. | .... | .... | .... | .... | 11.3 | 2.8 | + 7 | 68 | 22 | 98.6 | .... | .. | ... |
| A. S. | Mar. 13 | 21 | 20.3 | 31.7 | 64 | .... | .... | .... | .... | .... | .... | .... | 95 | 21 | 99.8 | 100 | 60 | ... |
| | 18 | 21 | 18.5 | 33.8 | 55 | 34.2 | .... | .... | .... | .... | .... | .... | 100 | 21 | 100.0 | .... | .. | ... |
| | 28 | 21 | 20.2 | 33.8 | 60 | 38.6 | 32.0 | 39.7 | 7.48 | 9.4 | 2.0 | .... | 85 | 20 | 99.8 | .... | .. | 1.9 |
| | April 1 | 45 | 21.5 | 33.2 | 65 | 40.0 | 35.0 | 39.2 | 7.46 | 10.5 | 2.5 | .... | 86 | 20 | 99.5 | 90 | 60 | 2.2 |
| I. S. | May 2 | 21 | 17.8 | 20.3 | 88 | 54.9 | 48.0 | 50.3 | 7.39 | 7.2 | 1.4 | .... | 102 | 22 | 99.4 | 130 | 100 | 3.0 |
| | 22 | 45 | 18.2 | 19.4 | 94 | 72.1 | 61.3 | 61.1 | 7.40 | .... | 1.2 | .... | 90 | 25 | 99.2 | 128 | 98 | ... |
| | June 25 | 45 | 16.7 | 18.0 | 93 | 73.5 | 67.0 | 61.5 | 7.37 | 6.5 | 1.0 | .... | 85 | 24 | 99.5 | 128 | 102 | 3.2 |

* All chemical data reported in this table were obtained from arterial blood.

† Other measurements of the blood of this patient were as follows: on December 28, lactic acid, 22.6 mg. per hundred cubic centimeters; serum chlorine, 97 mm.; serum protein, 6.14 per cent; on January 2, serum chlorine, 95.8 mm.; serum protein, 5.05 per cent; on January 6, lactic acid, 7 mg. per hundred cubic centimeters, serum chlorine, 97 mm., and serum protein, 5.55 per cent.

‡ Patient was receiving oxygen by nasal catheter

to its usual oxygen saturation. Clinically, the clearing of this patient's cyanosis when he was in an atmosphere containing a high degree of oxygen was definite.

4. There was a sharp rise in the carbon dioxide content and in the carbon dioxide curve of arterial blood when the patient was in an atmosphere containing a high degree of oxygen.

5. There was decreased pulmonary ventilation, lowered pulse rate and moderate increase in the vital capacity of the lungs.

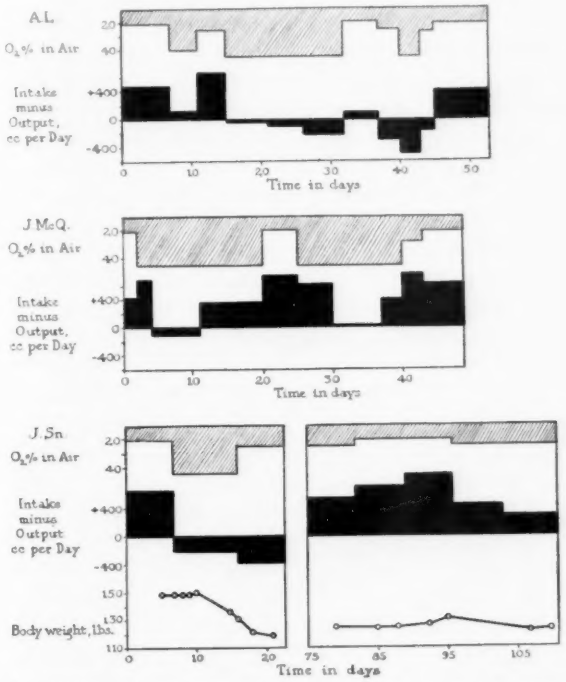


Chart 2.—Relation of the oxygen in the atmosphere to the balance of water in patients A. L., J. McQ. and J. Sn. (cases 1, 2 and 3). The upper (shaded) blocks show the percentage of oxygen in the atmospheric air; the lower (solid) blocks, the total intake of fluids minus the urinary output, the differences expressed as cubic centimeters per day.

6. In case 3 (J. Sn.) other measurements showed: (*a*) a slight increase in cardiac output, (*b*) a sharp fall in the lactic acid of the blood, from 22.6 mg. to a normal value of 7 mg. and (*c*) a lowered percentage of protein in the serum. An unexplained, profuse, intestinal hemorrhage, with considerable fall in the oxygen capicity, was probably concerned in this last change, owing to dilution of the blood serum.

M. G. (case 4) and I. B. (case 5) clearly represent a different group from the three first summarized. These were both cases of advanced and active rheumatic cardiac disease, with cyanosis, generalized passive congestion, edema and irregular fever. Subjectively, the patients were more comfortable and less dyspneic when they were in an atmosphere containing a high degree of oxygen; their cyanosis was somewhat improved, and in one case comparative measurements showed an increase in the arterial oxygen saturation from 84 to 93 per cent. In each case there was a moderate rise in the level of the carbon dioxide curve. Little change, however, occurred in the edema, and there was no tendency to diuresis. However, I. B. (case 5) was removed abruptly from the chamber when the atmosphere contained 45 per cent oxygen to the ward, where she rapidly went into collapse, with renal suppression for twenty hours, low blood pressure and profound cyanosis. The arterial oxygen saturation again fell to 84 per cent (this measurement was taken when the patient was receiving 4 liters of oxygen a minute by nasal catheter), the carbon dioxide dropped to the remarkably low value of 26.4 per cent by volume, and the arterial $p_H$ fell from 7.44 to 7.36. After the patient returned to the chamber in which the atmosphere contained 45 per cent oxygen, as noted in the clinical record, she quickly returned to her former condition. During the next twenty-four hours she passed 1,000 cc. of urine. Both of these patients showed lowered pulse rates while they were in an atmosphere containing a high degree of oxygen.

In the five cases cited, all of the patients may be said to have improved in an atmosphere containing 45 per cent oxygen. Other changes occurred, although not constantly: lowered respiratory rate, lowered body temperature, decreased basal metabolism, slightly raised arterial $p_H$ and decreased red blood cells and hemoglobin. There seemed to be no consistent alteration in the blood pressure.

Two patients J. Sr. (case 6) and A. S. (case 7) showed practically no reaction whatever to the increase in atmospheric oxygen. Case 6 was in a man of 54, with long-standing mitral stenosis, great cardiac enlargement and enlargement of the liver, but no edema or orthopnea. Clinically, he was moderately cyanotic, but this was evidently of venous origin, for when he was in the ward his arterial blood showed an oxygen saturation of 91 per cent or more. The development of a mild rhinitis and bronchitis, with a transient lowering of the carbon dioxide curve and of the vital capacity, seemed to be the only change while he was in the oxygen chamber. Subjectively, he was no better.

A. S. (case 7), a girl, aged 13, had congenital cardiac disease, which autopsy showed to be the tetralogy of Fallot, combined with patent ductus arteriosus. The case is being reported by Richards in further

detail elsewhere.[24] It is sufficient to note here that the arterial oxygen saturation of about 60 per cent was increased only to 65 per cent when she was in an atmosphere containing a high degree of oxygen, that there was no change in the carbon dioxide or in the urinary output, that the pulmonary blood flow was practically unaltered, and that subjectively she was not improved. She did not have edema at any time. She was not in the oxygen chamber long enough to rule out the possibility of a change in urinary output relative to the intake of fluid.

Finally, I. S. (case 8), a man, aged 29, with advanced chronic tuberculosis, including cavitation and paralysis of the right side of the diaphragm due to phrenicotomy, was also studied in the oxygen chamber. He was moderately cyanotic, markedly dyspneic and orthopneic and suffered greatly from a violent cough. On examination, his heart, except for the rapid rate, appeared to be normal. For the first six days he was kept in the oxygen chamber with the atmosphere containing 21 per cent of oxygen; then the oxygen was raised to 45 per cent and was maintained at that level for two months. Table 1 shows that there were a moderate improvement in the arterial oxygen saturation, an increased urinary output lasting about two weeks (though the patient never had any edema) and a remarkable rise in the carbon dioxide content of the blood of from 54.9 to 73.5 per cent by volume, giving an arterial carbon dioxide tension of 67 mm. Subjectively the patient was slightly better in an atmosphere containing a high degree of oxygen.

## COMMENT

In this somewhat varied group of cases of circulatory failure in which treatment with atmospheres containing 45 per cent oxygen was instituted, there are certain general tendencies that may be summarized:

The six patients who showed unmistakable clinical improvement, when breathing room air, were characterized by a low arterial oxygen saturation and a definitely increased saturation when in an atmosphere containing 45 per cent oxygen. With one exception, case 9, I. S., they had congestive cardiac failure. It seemed to be true also that marked subjective benefit came only after the oxygen saturation had been raised to 90 per cent or above. Clinically, the clearing of cyanosis in these patients occurred within a few hours after their introduction to the atmosphere containing a high degree of oxygen.

Conversely, the two patients whose arterial oxygen (and the cyanosis) was not appreciably altered showed no effects as a result of remaining in an atmosphere containing a high degree of oxygen.

24. Richards, D. W.: Congenital Heart Disease: Measurement of the Circulation, Arch. Int. Med. **47**:484 (March) 1931.

TABLE 2.—*Intake of Fluid and Output of Urine with Varying Determinations of the Oxygen Concentrations of the Respired Air*

| Case and Date | Days* | Ward or Oxygen Room | Per Cent of Oxygen in Atmosphere | Average Intake of Fluids per Day, Cc. | Average Output of Urine per Day, Cc. | Difference | Weight, Pounds | Average Pulse Rate |
|---|---|---|---|---|---|---|---|---|
| A. L. ..... | 7 | W | 21 | 1,124 | 643 | +481 | ... | 74 |
| June–July, | 4 | O | 40 | 628 | 495 | +133 | ... | 70 |
| 1929 | 4 | W | 25† | 1,080 | 387 | +693 | ... | 80 |
| | 6 | O | 45 | 672 | 1,030 | — 58 | ... | 94 |
| | 5 | O | 45 | 968 | 1,076 | —108 | ... | 92 |
| | 6 | O | 45 | 927 | 1,153 | —226 | ... | 90 |
| | 5 | O | 19 | 656 | 548 | +108 | ... | 68 |
| | 3 | O | 25 | 730 | 1,043 | —313 | ... | 66 |
| | 3 | O | 45 | 627 | 1,137 | —510 | ... | 58 |
| | 2 | O | 27 | 835 | 1,012 | —177 | ... | .. |
| | 8 | W | 21 | 1,400 | 986 | +414 | 109 | 67 |
| J. McQ..... | 2 | W | 21 | 900 | 475 | +425 | ... | 84 |
| August–September, 1929 | 2 | O | 45 | 1,145 | 450 | +695 | ... | 80 |
| | 7 | O | 45 | 1,449 | 1,587 | —138 | ... | 76 |
| | 9 | O | 45 | 1,272 | 899 | +373 | ... | 78 |
| | 5 | O | 20 | 1,263 | 510 | +753 | ... | 85 |
| | 5 | O | 45 | 1,250 | 613 | +637 | ... | 78 |
| | 7 | O | 45 | 1,267 | 1,226 | + 41 | ... | 74 |
| | 3 | O | 45 | 1,203 | 797 | +406 | ... | 70 |
| | 3 | O | 28 | 1,355 | 598 | +757 | ... | 72 |
| | 6 | W | 21 | 1,388 | 746 | +642 | ... | 76 |
| J. Sn..... | 7 | W | 21 | 1,349 | 689 | +660 | 149 | 108 |
| January–March, 1930 | 9 | O | 45 | 1,258 | 1,473 | —215 | 137 | 116 |
| | 7 | W | 25† | 1,050 | 1,436 | —386 | 119 | 110 |
| | 7 | W | 25† | 1,514 | 946 | +568 | 125 | 106 |
| | 7 | W | 21 | 1,393 | 675 | +718 | 125 | 112 |
| | 7 | W | 21 | 1,532 | 646 | +886 | 130 | 116 |
| | 7 | W | 25† | 1,371 | 907 | +464 | ... | 96 |
| | 8 | W | 25† | 1,297 | 982 | +315 | 122 | 114 |
| M. G..... | 7 | W | 21 | 1,557 | 454 | +1,103 | 139 | 86 |
| September–October, 1929 | 7 | O | 45 | 1,531 | 508 | +1,023 | ... | 76 |
| | 7 | O | 45 | 1,296 | 458 | +838 | ... | 80 |
| | 10 | W | 21 | 1,048 | 318 | +730 | ... | 100 |
| I. B..... | 5 | W | 21 | 1,000 | 550 | +450 | ... | 114 |
| September–October, 1929 | 1 | O | 21 | 1,260 | 650 | +610 | ... | 92 |
| | 5 | O | 45 | 1,148 | 420 | +728 | ... | 79 |
| | 5 | O | 45 | 1,188 | 458 | +730 | ... | 82 |
| | 6 | O | 45 | 1,280 | 594 | +686 | ... | 77 |
| | 1 | W | 21 | ..... | ..... | ..... | ... | 106 |
| | 1 | W–O | 21-40 | 1,105 | 235 | +870 | ... | 106 |
| | 6 | O | 45 | 1,240 | 673 | +567 | ... | 80 |
| | 7 | O | 40 | 1,291 | 683 | +608 | ... | 95 |
| | 8 | W | 25† | 913 | 394 | +519 | ... | 85 |
| | 8 | W | 25† | 1,088 | 221 | +867 | ... | 65 |
| J. Sr..... | 6 | W | 21 | 1,079 | 1,042 | + 37 | 145 | 74 |
| July–August 1929 | 3 | W–O | 21 | 1,057 | 833 | +224 | ... | 79 |
| | 7 | O | 20 | 1,134 | 1,079 | + 55 | ... | 72 |
| | 7 | O | 45 | 1,276 | 1,054 | +222 | ... | 70 |
| | 7 | W | 21 | 1,497 | 804 | +693 | 145 | 68 |
| A. S..... | 4 | W | 21 | 2,500 | 725+ | +1,775 | ... | 83 |
| April, 1930 | 4 | W | 21 | 2,725 | 431+ | +2,294 | ... | 85 |
| | 4 | O | 45 | 2,100 | 813 | +1,287 | ... | 86 |
| | 4 | W | 21 | 2,413 | 493+ | +1,920 | ... | 98 |
| I. S..... | 6 | O | 21 | 2,154 | 608 | +1,546 | 100 | 102 |
| May, 1930 | 6 | O | 45 | 1,421 | 808 | +613 | 100 | 84 |
| | 6 | O | 45 | 1,516 | 1,071 | +445 | 101 | 86 |
| | 6 | O | 45 | 1,483 | 767 | +716 | 101 | 90 |

* The total time during which a patient was studied was divided into short periods of a few days each.

† Patient in the ward, receiving oxygen by nasal catheter.

All patients who were clinically improved also showed a rise in the arterial carbon dioxide content and in the level of the carbon dioxide dissociation curves. There seemed to be some proportion between the extent of this rise and the increase in the arterial oxygen saturation (chart 1).

It is of interest to inquire whether the aforementioned changes in the gas content of the blood can be correlated with the alterations in pulmonary function that occur with increased oxygen concentration in the respired air.

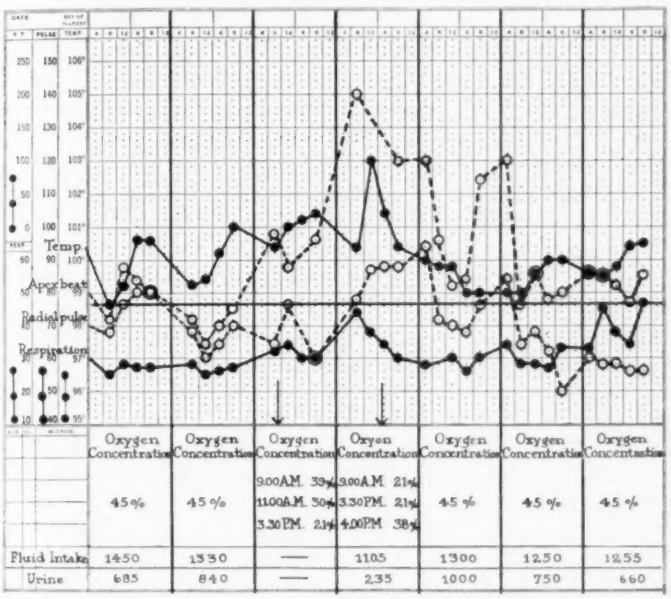


Chart 3 (case 5).—Hospital chart of patient I. B., showing changes following her withdrawal from an atmosphere containing a high degree of oxygen for twenty hours.

In cases of advanced cardiac failure, the defects in the anatomy and physiology of the lungs have been extensively investigated. The marked decrease in vital capacity has been associated by various writers with the suggestion of von Basch [25] that there is a stiffening of the lung (Lungenstarre) due to the congestion of the pulmonary blood vessels. In one of our cases (J. Sn.) during the stage of advanced congestive

25. von Basch, S. S. K.: Verschiedene Aufsätze im klinische und experimentelle Studien, Berlin, A. Hirschwald, 1891.

failure, the patient used his full vital capacity at each respiration. In such a situation, an increased ventilation can, of course, occur only by an increased rate of respiration. This phase has been investigated by Engelhard [26] and others. It has been shown by Binger [27] that the residual air is diminished relatively little in cases of congestive failure. In this condition Siebeck [28] has demonstrated the unequal aeration of different parts of the lungs. That there is a decreased capacity of the alveolar membranes for the diffusion of respired gases seems inevitable, but the extent of this effect is unknown.

The end-results of these various aspects of pulmonary dysfunction are dyspnea, with increase in ventilation, and in the advanced stages, more or less arterial oxygen unsaturation. The transport of carbon dioxide by the lungs is less embarrassed, and (as has been described) accumulation of carbon dioxide rarely occurs. The question of the actual nature of the stimulus in the "respiratory center" and the influence of the factors mentioned need not be discussed in the present connection.

It is clear that the chief difficulty in the pulmonary function in cardiac failure, namely, the transport of oxygen from the atmosphere to the blood, will at once be lessened when increased concentrations of this gas are breathed. Pulmonary (and arterial) blood will receive increased oxygen saturation, and at the same time pulmonary ventilation can decrease. As to the internal mechanism whereby the respiratory activity is lessened, our data do not contain anything new. Clearing of arterial anoxemia will presumably decrease the accumulation of acid in the tissues. In the one case in our series in which lactic acid was measured (case 3, J. Sn.), the value rapidly returned to normal following the inhalation of atmosphere containing a high degree of oxygen.

That the respiratory stimulus was generally decreased is evidenced by the lowered ventilation (chart 1), and that there was some diminution in the acidity of the tissues is suggested by the small but consistent lowering of the arterial hydrogen ion concentration.

Considered from the point of view of transport of oxygen and carbon dioxide, the altered pulmonary action resulting from inhalation of a high degree of atmospheric oxygen has in itself a consequence that may be related to the increased carbon dioxide levels of the blood which we have found. The high degree of oxygen in the inspired aid will evidently make possible the absorption of a sufficient amount of oxygen at a lower ventilation than previously. But decreased ventilation will in turn make more difficult the necessary elimination of carbon dioxide.

26. Engelhard, A.: Der Wert der Spirometrie für die Klinik der Herzkrankheiten, Deutsche Arch. f. klin. Med. **156**:1, 1927.

27. Binger, C. A. L.: Lung Volume in Heart Disease, J. Exper. Med. **38**:445, 1923.

28. Siebeck, R.: Ueber die kardiale Dyspnoe, Klin. Wchnschr. **8**:2121, 1929.

To meet this situation, two adjustments can be made: either an increase in pulmonary ventilation or an increase in the carbon dioxide levels of the blood and hence in the alveolar air so that a given amount of carbon dioxide can be eliminated at a lower ventilation than before. It seems that the state of equilibrium which these cases have assumed in an atmosphere containing a high degree of oxygen is of the latter type.

It should also be noted that as cardiac compensation is restored, a rise in the carbon dioxide levels has been observed to take place even in cases in which oxygen therapy was not given, although generally not to the same degree.

The mechanism whereby the rise in the carbon dioxide level actually took place is difficult to explain. The fall in the level of the lactic acid in the blood would be entirely inadequate to account for the total increase in carbon dioxide that we found in several cases. Further studies now in progress indicate that so far as the blood electrolytes are concerned, a rise in the serum bicarbonate is accompanied by a fall in the serum chloride.

One of the important features in the group of cases in which the patients were benefited by obtaining a high degree of oxygen is that clinical improvement continued steadily for a week or more after the patient's first introduction to an atmosphere containing 45 per cent of oxygen. The clearing of cyanosis and some relief in the urgency of the dyspnea began, as noted, within a few hours. Thereafter, the decrease in respiratory discomfort and especially the gradual disappearance of orthopnea were progressive for a number of days.

The most striking of the delayed effects in three cases were the diuresis and the disappearance of edema. Clinical improvement was most marked in these patients, all of whom had extreme congestive cardiac failure. Edema recurred when the oxygen was lowered to 21 per cent if compensation was not fully restored by that time.

For this apparent diuretic effect of an atmosphere containing a high degree of oxygen we are not able to offer an adequate explanation on the basis of the facts now at our disposal. That a better state of the circulation resulted from the improved transportation of oxygen is obvious, and that this must have been reflected in a more adequate renal function appears also to be a necessary inference. Other possibilites suggest themselves: (*a*) tissue capillaries, dilated because of anoxemia (Krogh[29]), with consequent alteration in permeability (Landis[30]),

29. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Conn., Yale University Press, 1922.

30. Landis, Eugene M.: Micro-Injection Studies of Capillary Permeability: III. The Effect of Lack of Oxygen on the Permeability of the Capillary Wall to Fluid and to the Plasma Proteins, Am. J. Physiol. **83**:528, 1928.

returned to their normal state; (*b*) increased capillary and venous pressures returned to normal; (*c*) some other alteration may have taken place in the water balance of the tissues, following exposure to a high degree of oxygen, dependent on the general electrolyte changes of which the rise in the carbon dioxide curve was a part. It is evident that a more complete metabolic study should be made of this type of diuresis.

Our studies of the dynamics of circulation were not sufficiently comprehensive to permit conclusions as to the possible effects of treatment with oxygen in this regard. The difficulty of making satisfactory determinations of cardiac output in cases of cardiac failure is well known; in four cases we were able to make a fairly reliable measurement of this function namely, in the cases of J. Sr. and A. S. (who were not improved clinically), J. Sn. and I. S. All four showed a small rise in cardiac output following the inhalation of a high degree of oxygen, the change in each case being about at the upper limit of the error of the method. There were no consistent changes in arterial blood pressure. The pulse rate was lowered. Measurements were not made of the blood volume, blood velocity and venous pressure.

## SUMMARY

1. Eight patients suffering from various forms of circulatory failure, with cyanosis, were treated in an oxygen chamber for from three to sixty days, the oxygen in the atmosphere being kept at 45 per cent.

2. The five patients who had congestive cardiac failure with arterial anoxemia were benefited by an atmosphere containing a high degree of oxygen. The striking objective changes were: increased arterial oxygen saturation with decrease of cyanosis, diminished pulmonary ventilation and rise in the carbon dioxide levels. Subjectively, there was relief from dyspnea and orthopnea.

3. Three of the patients experienced marked diuresis and disappearance of edema while breathing a high degree of oxygen. The edema returned when the degree of oxygen was lowered, and again disappeared when the oxygen was increased, as long as cardiac insufficiency was present.

## REPORT OF CASES

CASE 1.—*History.*—A. L., a colored woman, aged 55, was admitted to the hospital for the sixth time during the past five years on April 29, 1929, with a diagnosis of cardiac insufficiency and hypertrophy, auricular fibrillation, chronic myocarditis and general arteriosclerosis. She was in a severe state of decompensation. Ten days before admission she caught a cold, which was followed by dyspnea, cough, frothy sputum and swelling of the extremities.

*Physical Examination.*—The patient was old-looking, markedly uncomfortable, dyspneic and orthopneic, and had an anxious expression. The heart was greatly enlarged to the left and to the right, fibrillating, with a rate between 90 and 100;

the pulse was very feeble. A loud systolic murmur was heard over the precordium. The blood pressure was 140 systolic and 80 diastolic. Numerous sibilant and a few moist râles were heard over the lungs. The liver was palpable midway to the umbilicus. There was moderate edema of the extremities. The Wassermann reaction of the blood was negative. The blood urea was 0.40 Gm. per liter. The excretion of phthalein was 35 per cent in two hours and a quarter.

*Course.*—The patient improved temporarily after phlebotomy and the administration of salyrgan and digitalis. At the end of six weeks' residence in the hospital she was still uncomfortable, with marked dyspnea and epigastric distress. The edema in the legs was increased, while fluid was accumulating in the abdomen and chest. On June 10, she was transferred to the oxygen chamber, in which the atmosphere contained an oxygen concentration of 45 per cent. Striking improvement occurred in her general well-being within three hours and relief from dyspnea within six hours. During the first four days in the oxygen chamber, she was more comfortable and entirely relieved from orthopnea, though the epigastric discomfort persisted. She was then removed from the chamber, and in the next twenty-four hours the pulse rate rose from 70 to 90, the temperature from 99 to 100 F. and the rate of respiration from 20 to 38. Dyspnea and orthopnea returned. For part of the time during the next four days she received oxygen by nasal catheter, obtaining slight relief, and part of the time she spent in an oxygen tent, with moderate relief. On June 21, she was returned to the oxygen chamber, the oxygen concentration being 45 per cent. On the following day the dyspnea and orthopnea were greatly decreased. The patient was kept in this atmosphere for seventeen days, at the end of which time her condition was improved; there was no orthopnea, little epigastric distress and a slight cough. The edema of the legs and the ascites had decreased considerably, but had not disappeared entirely. The oxygen concentration in the chamber was then lowered to 19 per cent for five days. Dyspnea and orthopnea reappeared and the patient's vital capacity was only 520 cc. The liver was palpable almost to the umbilicus. There was a reaccumulation of edema, and decrease of the urinary output. In the next three days with the oxygen concentration at 25 per cent, she showed definite improvement, and the urinary output increased. The concentration of oxygen was then raised to 42 per cent, and the patient experienced a return of general comfort and increased diuresis. During the three days before she was returned to the ward, the oxygen concentration was gradually lowered, and she was removed from the chamber with no increase in dyspnea or orthopnea. In the ward she continued to improve, her vital capacity increasing to 940 cc. The urinary output was strikingly increased over the intake of fluids during the patient's residence in an atmosphere containing a high degree of oxygen and lowered during the periods when she inhaled a low amount of oxygen. She was finally able to sit in a chair, and on August 1 she left the hospital much improved. Later, while at home, decompensation again developed, dyspnea and edema increased progressively, and she died on October 29.

CASE 2.—*History.*—J. McQ., a white man, aged 53, was admitted to the hospital on Aug. 13, 1929, with diagnosis of cardiac insufficiency and hypertrophy, aneurysm of the ascending aorta, chronic cardiac valvular disease, aortic and mitral insufficiency, chronic myocarditis, general arteriosclerosis and hydrothorax on the left side. For the preceding three years he had suffered from attacks of epigastric pain, radiating to the sternum and interscapular region, accompanied by increasing dyspnea, orthopnea and swelling of the extremities. During the six weeks before the patient's admission the symptoms had become worse, and the

patient entered the hospital for the third time. There was no history of rheumatic or syphilitic disease. The Wassermann reaction of the blood was repeatedly negative. The blood urea was 0.38 Gm. per liter.

*Physical Examination.*—The patient was tall, gaunt and middle-aged, dyspneic, slightly cyanotic and markedly prostrated. The heart was enormously enlarged, and the left border could be felt in the anterior axillary line. There was marked systolic expansion of the wall of the chest on both the left and the right side. There was a continuous double murmur in the aortic area, transmitted into the neck and audible at the apex. The blood pressure was 130 systolic and 30 diastolic. On the previous admission fluoroscopy had showed marked extensive pulsation of the right margin of the heart shadow and intrapericardial aneurysm. The liver was palpable below the costal margin. There were pitting edema in the lower half of both legs and signs of fluid in the lower half of the left side of the chest. The basal metabolic rate was + 29 per cent. Two days after admission, the patient's vital capacity was 1,510 cc.

*Course.*—After three days in the ward, during which the patient failed to improve and continued to be critically ill, he was transferred to an oxygen chamber with a concentration of oxygen of 45 per cent. On the following day, dyspnea was relieved, cyanosis was absent, and he was much more comfortable. The vital capacity at this time measured 2,050 cc. Two days after he had entered the oxygen chamber the urinary output rose from 500 to 1,700 cc. The temperature, pulse rate and respiratory rate gradually decreased. General improvement continued during the following eighteen days' residence in the oxygen room; the vital capacity rose to 2,600 cc., and the edema of the legs diminished.

The oxygen concentration in the chamber was then lowered gradually in forty-eight hours to 20 per cent and was maintained at that level for four days. The patient's condition became progressively worse, with increased dyspnea, cyanosis, rapid pulse and respiration and rise in temperature, accompanied by a fall in urinary excretion and a drop in vital capacity to 1,490 cc. The oxygen concentration was again raised to 45 per cent with a gradual return, within the next week, of the patient's previous comfortable condition. During the following ten days diuresis continued, until he was completely free from edema of the extremities and from fluid in the chest. The oxygen concentration was again gradually lowered to 21 per cent in forty-eight hours, and the patient was removed to the ward. There was a temporary slight return of dyspnea and general discomfort, with elevated pulse and respiratory rates and a fever which continued for three days. During the next month he remained in the ward in fairly good condition without oxygen, but he had occasional attacks of dyspnea. At the end of this time the vital capacity was 1,510 cc. Later he failed gradually; he became increasingly dyspneic and cyanotic, had severe substernal pain, and required large amounts of morphine. He died on December 14.

Case 3.—*History.*—J. Sn., a white man, aged 30, was admitted to the hospital on Dec. 20, 1929, with the diagnosis of interstitial pneumonia, cardiac hypertrophy and insufficiency, adherent pericardium, ascites, generalized edema, atrophic rhinitis, chronic pharyngitis and intestinal hemorrhage. Seven years before admission the patient had been troubled with nasal exudate, dryness of the throat and cough. For five years there had been progressive dyspnea on exertion, fatigue, cyanosis, productive cough and clubbing of the fingers. He had been confined to his bed for much of the time during the past year, and for a month there had been increasing generalized edema. He had been at Bellevue Hospital, but at the suggestion of Dr. James A. Miller, had been transferred to the Presbyterian Hospital for further treatment.

*Physical Examination.*—The patient was dyspneic and orthopneic, with a puffy face, generalized edema and marked grayish cyanosis of the skin and mucous membranes. The fingers were clubbed, and the nail-beds were markedly cyanosed. The nasal mucous membranes were atrophic and there was much crusting; the pharynx was congested. There was marked dulness over the upper lobes of both lungs, with harsh bronchial breathing and many moist râles. The heart was enlarged to the left and right, the rate was rapid with a gallop rhythm during inspiration, and the pulmonic second sound was accentuated. The liver was enlarged, and the edge of the spleen was palpable. There was moderate generalized peripheral edema and ascites.

Examination of the blood showed: red cells, 6,500,000, and hemoglobin, 108 per cent (Sahli); the Wassermann reaction was negative. The blood urea was 0.35 Gm. per liter. Examination of the sputum was negative for tuberculosis. A roentgenogram of the chest showed a dense infiltrative process spreading upward and laterally from the hilus on both sides. Fluoroscopy of the heart showed general enlargement, a dilated conus and slight fixation of the pericardium with change of position.

*Course.*—During the patient's first week in the ward, he became definitely worse; cyanosis, edema and respiratory discomfort increased. His temperature varied between 101 and 102 F. On December 28, he was transferred to an oxygen chamber containing 45 per cent of oxygen; subjective improvement and decrease of cyanosis were noted within a few hours. The urinary output was more than doubled on the second day after transfer from the ward, and this increase was maintained (on the average) for the next two weeks. On his fifth day in the oxygen chamber an intestinal hemorrhage suddenly developed, and in the next thirty-six hours the patient lost about 1.5 liters of blood. He was drowsy, seemed weak and had a marked tachycardia. His fever, which since admission had continued its gradual rise, dropped to normal by crisis at the end of the second day of hemorrhage (Jan. 2, 1930). The bleeding thereafter gradually stopped; its cause was not found. On January 7, he was again transferred to the ward, and oxygen was administered by nasal catheter at about 4 liters per minute. Diuresis continued, and by January 14 all edema had disappeared. The signs in the lungs seemed to clear slightly. A moderate cyanosis persisted. This regimen was continued for the next two months. Other medication—potassium iodide in large doses and ethyl iodide by inhalation—was tried, with no apparent effect. On March 14, the administration of oxygen was discontinued; for the next two weeks his cough and cyanosis grew worse, and the temperature rose and the pulse rate increased steadily. The urinary output was decreased, and the weight increased, though there were no definite signs of peripheral edema. The administration of oxygen by nasal catheter again produced increased urinary output and the loss of 9 pounds (4.1 Kg.) in weight. This treatment was continued for two months longer, when the patient was transferred to the Montefiore Hospital for a month, during which time no oxygen was administered. He was then (July, 1930) ambulatory and well enough to go home. At present, May, 1931, he is at home ambulatory, but not able to work.

Case 4.—*History.*—M. G., a white woman, aged 52, was admitted to the hospital on June 22, 1929, with the diagnosis of cardiac insufficiency and hypertrophy, auricular fibrillation, chronic cardiac valvular disease, mitral stenosis and insufficiency, aortic insufficiency, hydrothorax and ascites. For the past ten years the patient had suffered from breathlessness on exertion. One year before admission, she had been treated in the hospital for her first attack of cardiac

decompensation. For seventeen days prior to the present admission she had complained of severe dyspnea, orthopnea, palpitation and swelling of the extremities.

*Physical Examination.*—On examination, the patient was moderately dyspneic, slightly cyanotic, anxious and distressed. The heart was markedly enlarged to the right and to the left, the action was irregular, the rate at the apex was 84, the radial rate was 78; a systolic murmur was heard at the apex and a diastolic murmur at the left border of the sternum. The blood pressure was 232 systolic and 104 diastolic. The lungs showed signs of fluid in the right side of the chest. The liver was palpable 7 cm. below the costal margin. There was moderate edema of the thighs and the ankles. The temperature ranged between 100 and 102 F. The Wassermann reaction of the blood was negative. There was a 40 per cent excretion of phthalein in two hours and a quarter. The blood urea was 0.32 Gm. per liter.

*Course.*—During fourteen weeks' rest in bed in the hospital the patient made no improvement. She was transferred to the oxygen chamber with the oxygen concentration at 45 per cent, where she remained for fifteen days, with increased comfort and diminished dyspnea, but without disappearance of the edema. At the end of this time, the oxygen concentration was lowered to 30 per cent for twenty-four hours, and the patient was removed from the chamber. During the following twenty-four hours she experienced increased dyspnea, lessened comfort and elevation of the pulse rate. During the next three weeks her condition grew slowly worse, requiring three thoracenteses. She then remained in about the same condition until discharged as a bed case, on December 2. She was last heard from in June, 1930, when she was "doing as well as could be expected."

This patient appeared to have had an active rheumatic myocarditis, accompanied by constant fever. She was more comfortable in the oxygen chamber, with lessened dyspnea and orthopnea. When she was in an atmosphere containing a high degree of oxygen, although there was no noteworthy diminution in the edema of the legs, she did not require thoracentesis, whereas after she left the chamber thoracentesis was required at almost weekly intervals.

CASE 5.—*History.*—I. B., a white woman, aged 32, was admitted to the hospital on Sept. 21, 1929, with the diagnosis of cardiac insufficiency and hypertrophy, chronic cardiac valvular disease, mitral stenosis and insufficiency, auricular fibrillation and acute rheumatic fever. Following an attack of pneumonia twelve years before, the patient began to experience shortness of breath after exertion. Two years later, she had rheumatic fever with swollen joints. For the five years before admission there had been symptoms of progressive decompensation. For five weeks she had suffered from increasing dyspnea, pain in the chest and swelling of both legs.

*Physical Examination.*—The patient had deep red cheeks, and marked cyanosis of the lips and nail-beds; she was in great distress, being very dyspneic and prostrated. The heart was enormously enlarged; the left border could be felt in the anterior axillary line. The rate at the apex was 140, that at the wrist, 80. The first sound at the apex was replaced by a loud, metallic, systolic blowing murmur, followed by a soft diastolic murmur. The blood pressure was 150 systolic and 80 diastolic. Examination of the abdomen showed a large, tender, pulsating liver palpable at the umbilicus. Numerous crackling râles were heard

over both sides of the chest posteriorly. There was marked edema of the sacrum and the legs. Examination of the blood revealed: red blood cells, 6,740,000, and hemoglobin, 145 per cent. The temperature ranged between 100 and 102 F. A culture of the blood was sterile.

*Course.*—On September 26, after five days of routine treatment in the ward had produced no improvement, the patient was put in an oxygen chamber, in which the concentration of oxygen was 21 per cent; after eighteen hours there was no relief. Oxygen concentration was then increased to 45 per cent and was maintained at that level for seventeen days. After the increase in atmospheric oxygen, the patient was subjectively very much improved. Her breathing became quiet, with little dyspnea, and the cyanosis was much diminished. No effect was noticed on the urinary output, the size of the liver or the edema of the extremities. In three days the hemoglobin decreased to 125 per cent, and the red blood cells to 5,560,000; in six days the former was 110 per cent and the latter, 5,460,000. At the end of seventeen days, the oxygen concentration was lowered to 21 per cent in six hours, and the patient was removed to the ward. She became worse almost at once, with profound cyanosis, sweating and dyspnea. She grew progressively weaker and more prostrated. The pulse rate was very faint. The systolic pressure was 90, and the diastolic could not be counted. She voided no urine, and none was obtained from the bladder on catheterization. She was apparently in a state of shock. Twenty-four hours after she had been moved to the ward, she was returned to the oxygen chamber; improvement was noticed almost at once, with increased strength, easier respiration and better color. After four hours her blood pressure was 120 systolic and 73 diastolic. She voided 125 cc. of urine at about the same time. On the following day, she voided 1,000 cc. of urine. At the end of three days, her condition approximated that present before her removal from the oxygen chamber. On October 26, after seven more days in the oxygen chamber, the percentage of oxygen was gradually reduced, and on October 29, she was returned to the ward. She held her own fairly well for a while, receiving oxygen by nasal catheter, but then failed rapidly, and died on November 24.

CASE 6.—*History.*—J. Sr., a white man, aged 54, was admitted to the hospital on May 25, 1929, with the diagnosis of cardiac insufficiency, chronic cardiac valvular disease, mitral stenosis and insufficiency and auricular fibrillation. For the four years before admission the patient had complained of gradual increase of breathlessness on exertion, with swelling of the abdomen and slight edema of the ankles. He had been in another hospital eight months previously with decompensation, and had been discharged after an eight months' stay. The present attack of dyspnea and the appearance of some edema had begun three weeks before admission.

*Physical Examination.*—The patient was slightly dyspneic and moderately cyanotic, but he had no orthopnea, even when he was lying flat in bed. The heart was enlarged 13.5 cm. to the left in the sixth space, and was slowly fibrillating, with a low systolic and soft diastolic murmur at the apex. The blood pressure was 118 systolic and 94 diastolic. The liver was palpable at the umbilicus. There was slight edema of the extremities. The basal metabolic rate ranged from +2 to +9 per cent, and the vital capacity was 3,300 cc. The Wassermann reaction of the blood was negative. The blood urea was 0.22 Gm. per liter.

*Course.*—The patient was kept at rest in bed in the hospital for three months. The edema disappeared during the first week, and he improved slowly and was up an hour a day in a chair. He was transferred to the oxygen chamber on July 31, in the hope that further improvement in his cardiac reserve could be

obtained. During the first week in the chamber, with the oxygen concentration of the atmosphere at 21 per cent, there was no significant change. The vital capacity dropped gradually to 2,790 cc. The oxygen concentration was then increased to 45 per cent without any improvement in the patient's condition. The vital capacity was 2,620 cc. While the patient was in the chamber, a cold with a cough developed, and he felt worse for several days. Respiration became wheezing, and the lungs were filled with sibilant râles. After eight days in the chamber with the oxygen concentration at 45 per cent, the patient was returned to the ward. Two days later his vital capacity was 2,720 cc. He remained in the hospital for three months after removal from the oxygen chamber, without change in his condition. When treatment with oxygen was begun the patient had no edema. He had moderate cyanosis, venous in origin, which was not greatly diminished in the oxygen chamber.

Thereafter, the disease ran a long course while the patient was in the hospital, and there were several pulmonary infarcts. He was finally discharged as a bed case on November 9. He died at home on Feb. 13, 1930.

CASE 7.—*History.*—A. S., a white girl, aged 13, was admitted to the hospital on March 7, 1930, with the diagnosis of cardiac insufficiency and hypertrophy, congenital pulmonary stenosis, defect of the intraventricular septum, transposition of the great arterial trunks, hypertrophy of the right ventricle, patent ductus arteriosus and abscess of the brain with rupture into the right lateral ventricle. Since the age of 3 years, the patient had been markedly cyanosed, and had suffered increasingly from dyspnea on exertion. She had had recurrent attacks of pains in the joints. Her fingers had been clubbed for at least five years.

*Physical Examination.*—Examination revealed a small, thin girl, lying quietly in bed, hyperpneic but not dyspneic. There was extreme cyanosis of the skin and mucous membranes; the lips and tongue were almost black. There was clubbing of the fingers and toes. The heart was moderately enlarged, with a systolic shock at the apex, a thrill over the third and fourth left interspaces, and double murmurs at the apex and base. The second pulmonic sound was sharply accentuated. The liver and spleen were not felt. There was no peripheral edema. Examination of the blood showed: red cells, 10,900,000, and hemoglobin, 160 per cent. The Wassermann reaction of the blood was negative.

*Course.*—The patient was able to walk about the wards without discomfort. After three weeks, she was transferred to the oxygen chamber in which the atmosphere contained 45 per cent oxygen, and was there for four days. No significant change in her clinical condition was noted. She was discharged from the hospital on April 6. On May 7, she was readmitted, with a progressive paralysis of the left side, and she died on May 12. The postmortem observations are indicated in the foregoing diagnosis.

CASE 8.—*History.*—I. S., a white man, aged 29, a salesman, was admitted to the hospital on April 28, 1930, with the diagnosis of far advanced chronic pulmonary tuberculosis; the upper lobe of the right lung showed an excavation. Right phrenicectomy had been performed. The patient had complained of cough for two years and he had had three pulmonary hemorrhages during the year before admission. Nine months before, dyspnea on exertion developed; the patient lost weight and more sputum was raised. He entered Bellevue Hospital on Jan. 1, 1930, and was under treatment there for five months. He was found to have advanced tuberculosis, with a large cavity in the right lung. During the next two months, artificial pneumothorax was performed by successive injections of air, but this was discontinued following renewed hemoptysis. On March 11, right

phrenicectomy was performed; two weeks later, a roentgenogram of the lung showed that the cavity had diminished one-half and the patient's general condition was slightly improved. He was transferred to the Presbyterian Hospital for treatment in the oxygen chamber.

*Physical Examination.*—The patient appeared chronically ill, poorly nourished, cyanotic, dyspneic and orthopneic, and he was suffering from violent spasms of slightly productive cough. There was moderate cyanosis of the lips and mucous membranes. On the left side of the chest there were harsh breath sounds over the midlung, with many moist râles; on the right, flatness at the base of the lung (relaxed diaphragm), scattered moist râles with dulness over the upper lobe and an area of amphoric breathing anteriorly. The heart was not enlarged; the sounds were rapid and loud. The patient weighed 100 pounds (45.4 Kg.). Examination of the blood revealed: red cells, 6,340,000, and hemoglobin, 121 per cent (Sahli). The blood urea was 0.21 Gm. per liter. Urinalysis gave negative results. On several occasions, examination of the sputum was positive for tuberculosis. A roentgenogram showed dense infiltration over the upper lobe of the right lung, with a cavity at the apex, and fresh infiltration in the left lung.

*Course.*—The patient was in the oxygen chamber throughout his stay of eleven weeks in the hospital. During the first week the oxygen in the atmosphere was kept at 21 per cent. The patient was greatly exhausted by a racking cough. His appetite was poor, and he vomited frequently. The oxygen was then raised to from 45 to 50 per cent and was maintained at that level. The cyanosis cleared up almost at once and did not recur. During the succeeding weeks, clinically, there seemed to be a slow but definite improvement. There were less cough and less dyspnea, the patient was not orthopneic, and he gained 4 pounds (1.8 Kg.). The red blood cells decreased from 6,340,000 to 5,400,000, and the hemoglobin from 121 to 95 per cent. The vital capacity decreased from 1,500 cc. to 1,000 cc. There were fewer râles in the lungs. A roentgenogram showed that there were no marked changes in the lungs. During the week of May 26 to June 1, the patient had several small hemoptyses. Throughout his stay in the hospital his temperature remained between 99 and 100 F. During the last five days (from July 10 to 14) the oxygen was gradually reduced in the chamber to atmospheric level, and the temperature raised; there were no untoward symptoms, and on July 15, he was again transferred to the Bellevue Hospital.

# Book Reviews

RHEUMAPROBLEME. GESAMMELTE VORTRÄGE GEHALTEN AUS DEM II. ARTZEKURSUS DES RHEUMA-FORSCHUNGS INSTITUTS AM LANDESBAD DER RHEINPROVINZ IM AACHEN. Volume 2. Price, 12 marks. Pp. 176. Leipzig: Georg Thieme, 1931.

This volume contains lectures on chronic rheumatism given to physicians.

The pathogenesis and clinical manifestations of chronic diseases of the joints are discussed by Prof. Herbert Assman of Leipzig. He considers the two types of chronic arthritis — infectious and ostearthritis — and logically advises that as ostearthritis is not infective, the better term is ostearthrosis.

Prof. Richard Birling of Frankfort discusses experimental infective arthritis. He supports the generally accepted view that chronic infective arthritis, as found in man, has not been reproduced experimentally. He relates in detail the changes in the joints observed in horses used for the preparation of diphtheria antitoxin.

Roentgenograms of acute and subacute joint inflammation are presented by Prof. Gottfried Boehm of Munich. The inflammation of joints associated with acute infection is discussed in detail.

Prof. Christian Bruhn of Dusseldorf presents a complete chapter on the importance of stomatological studies and their possible relation to chronic rheumatism.

The differential diagnosis of rheumatism from certain other diseases in children is discussed by Prof. Albert Eckstein of Düsseldorf. This chapter is well illustrated by roentgenograms.

Prof. Anton Fischer of Aix-la-Chapelle stresses the importance of medical experts in national health insurance in order to secure a proper diagnosis and prognosis in the various disturbances of the joints.

The chapter on the influence of therapeutic measures on infectious arthritis by Dr. Heinz Gehlen of Aix-la-Chapelle deals chiefly with the teeth and tonsils as foci of infection and the therapeutic value of their removal.

The doctrine of focal infection in rheumatic diseases given by Prof. Siegfried Graff (Hamburg) is presented, as the author states, from a theoretical standpoint. He discusses the etiology of rheumatism, or at least the symptom complex that is referred to as rheumatism.

So-called rheumatism of the spine is presented by Dr. Walter Krebs of Aix-la-Chapelle. Following the present conception, he considers two types: spondylarthritis ankylopoietica, synonymous with the "poker spine" in the American literature, and spondylitis deformans, synonymous with ostearthritis. The former he attributes to an infection; the latter, to acute trauma or overuse.

There is a brief chapter on the heart and chronic rheumatism by Prof. Franz Kulbs (Cologne).

Dr. Stephan Loewe (Breslau), consultant to a dental institute for the treatment of patients carrying social insurance, which includes dental care, is optimistic over the value of removing dental infection in chronic rheumatism.

The present state of knowledge regarding the etiology of infectious rheumatism is reviewed by Prof. Paul Manteufel (Dusseldorf). He gives a complete review of the literature, stating that in Germany the question of a specific rheumatic virus is treated in a "stepmotherly manner." He questions the probability of a specific micro-organism. This chapter is excellent.

Prof. Walther Muller (Konigsburg) discusses the biologic basis of disturbances of the joints.

Nutrition and nutritional disturbance and their relation to so-called rheumatism are presented by Prof. Hermann Strauss (Berlin). He takes up calcium, phosphorus, nitrogen and sugar metabolism and the relation of obesity to ostearthritis. He also discusses the basis of various dietary procedures.

The endocrine glands and diseases of the joints are discussed in detail by Prof. S. J. Thannhauser (Freiberg). He also reviews the literature on the rôle of the endocrines in Perthes', Köhler's and Kienböck's diseases. This chapter is profusely illustrated.

These discussions have been prepared with great care. The literature is thoroughly reviewed, and, in addition, personal experience is recorded. The references in the bibliography will be of great assistance to those who wish to study the sources of information. This volume is a valuable addition to the literature or chronic diseases of the joints.

TEXTBOOK OF SURGERY. By JOHN HOMANS. Price, $9. Springfield, Ill.: Charles C. Thomas, 1931.

This is a well bound volume of nearly 1,200 pages, evidently intended as a student's textbook in surgery. There are more than 500 illustrations, mostly of a schematic sort, but which amply demonstrate the points intended. It is a rather ambitious attempt to cover not only the field of general surgery, but all of the surgical specialties as well, including ophthalmology, otolaryngology, gynecology and urology.

The work is assembled in rather an original manner, being compiled from either the lecture notes or the complete written lectures of various members of the department of surgery of Harvard Medical College, and therefore represents the collaboration of an extremely prominent group of specialists. Dr. Homans says in the introduction that the material with which he worked was exceedingly varied; some of it consisted of rather sketchy lecture notes which he amplified into the text, while some of it was received with the text nearly as it is printed.

The work is decidedly provocative, and the reviewer cannot help being impressed with the refreshing newness of the manner of presentation as well as with a number of glaring faults. The style is breezy and makes entertaining reading, being practical in the extreme. All unnecessary classifications are left out, and the all too brief descriptions of diseases and their treatment make a lasting impression on the reader's mind because of the often colloquial English in which they are couched. Even the names of conditions are at times withheld (as in carcinoids of the appendix), although a number of lines are devoted to a description of the condition.

The routine treatment of many surgical diseases has been handed down from one textbook to another, even compiled for generations, and in that sense this work represents a decided advance, because it is based on the extraction of real medicine from the material presented to students and probably not so much on the diseases and complications from other textbooks. For that reason the more common conditions receive their share of emphasis, often at the expense of certain rarer diseases and complications. One cannot help feeling that a student who has studied this work carefully would probably not stand high in a competitive examination, but would make an eminently practical physician.

Many of the statements made in the book would seem, in the opinion of some surgeons at least, to be categorically wrong. This is especially true of the choice of treatment, as in the majority of cases the author attempted to tell the student only the best treatment, and such matters are often open to discussion. An example is the entire omission of Sayre's dressing as a treatment for a fractured clavicle, or the statement that the worsted truss will cure infantile hernia, whereas, in the opinion of most students of hernia, it is worthless; also, the statement that most retroperitoneal tumors are inoperable is untrue. Such criticisms could be multiplied almost indefinitely, but the reviewer feels that this should not prevent a wide adoption of the book as a surgical textbook on account of its many advantages.

One of the interesting features of the book is the author's contribution to medical history. Nearly every appliance, disease or treatment for disease is traced back to its original source, and, as a consequence, the amount of historical

material presented is truly astounding. In many cases, also, this is offered in such a way that it has a direct bearing on the treatment and diagnosis and therefore does not represent something more for the student to learn.

CLINICAL DIAGNOSIS BY LABORATORY METHODS. By JAMES CAMPBELL TODD, PH.B., M.D., Late Professor of Clinical Pathology, University of Colorado School of Medicine, and ARTHUR HAWLEY SANFORD, A.M., M.D., Professor of Clinical Pathology, University of Minnesota (Mayo Foundation); Head of Section on Clinical Laboratories, Mayo Clinic. Seventh edition, thoroughly revised. Cloth. Price, $6. Pp. 765, with 347 illustrations, 29 in color. Philadelphia: W. B. Saunders Company, 1931.

This text, now published in the seventh edition with Sanford as co-author, has for many years served a useful purpose in courses of laboratory instruction as a text and in clinical laboratories as a guide. It ranks with other American texts, such as that of Cummer, in the choice and extent of material presented. The eleven chapters, exclusive of the introductory paragraphs on the use of the microscope, cover adequately routine examinations of the sputum, the urine, the blood, the gastric and duodenal contents, the feces, certain animal parasites, exudates and tissue fluids, miscellaneous examinations, serologic methods, bacteriologic technic and vaccines and biologic tests of the skin. A short appendix is devoted to instructions of a general character, including the preparation of solutions. The subject material is well organized and meets adequately the demands of a text for students and of a guide for clinical laboratories.

THROUGH THE ALIMENTARY CANAL WITH GUN AND CAMERA. A FASCINATING TRIP TO THE INTERIOR. Personally conducted by GEORGE S. CHAPPELL. Introduction by Robert Benchley. Cloth. Price, $2. Pp. 231, with illustrations. New York: Frederick A. Stokes Company, 1930.

Dr. Walter Traprock, author of the famous "Traprock Trilogy," herein presents an amusing, farcical tale of an excursion through the human alimentary tract as far as the colon and return. The return journey is equally humorous, but is decidedly more perilous in every respect. "The Calomels Are Coming" is the theme song. The illustrations are cleverly adapted to the text and add greatly to the enjoyment of the book, which is worth a few hours of anybody's time.

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